EXPERT OPINION

Latest approaches for the treatment of obesity

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Introduction: Obesity is a body weight disorder characterized by excess adiposity that increases the risk for developing co-morbidities such as type 2 diabetes. A large medical need exists for new anti-obesity treatments capable of promoting 10% or greater weight loss, with minimal side effects.

Areas covered: The authors describe the application of monogenic forms of rare obesity and genome-wide association studies in selecting critical pathways for drug discovery. Furthermore, they review in detail several pathways and pharmacological targets in the central nervous system (e.g., the leptin-melanocortin axis, the opioid system, GLP-1/GLP-1 system, and FGF21/FGFR1c/β-Klotho axis) that play an important role in the regulation of feeding behavior and energy homeostasis. Special focus is given to new strategies that engage well-known targets via novel mechanisms in order to circumvent issues seen with previous drug candidates that failed in the clinic. Finally, the authors discuss the recent developments around fixed-dose combinations, targeted polypharmacology, and non-traditional combinations of drugs and devices.

Expert opinion: The future for new weight-loss approaches to treat obesity looks promising. Current therapies have shown modest effects on weight loss in the general obese population but will have greater impact in smaller homogeneous sub-populations of obese subjects using personalized medicine. Drug combinations that target multiple, complementary pathways have the potential to promote double-digit weight loss in a broader, heterogeneous patient population. Furthermore, the development of advanced subcutaneous delivery technologies has opened up opportunities to develop breakthrough peptide and biologic agents for the treatment of obesity.

Keywords: central nervous system, devices, FGF21, FGFR1c/β-Klotho, GLP-1, GLP-1R, LepRb, leptin system, MC4R, melanocortin system, microbiome, obesity

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1. Introduction

The regulation of body weight is a complex process involving multiple metabolic pathways in both the central nervous system (CNS) and the periphery. Maintenance of a normal body weight as defined by a body mass index (BMI) ≤ 25 kg/m^2 requires a balance between energy intake and energy expenditure. A state of positive energy balance exists when energy intake exceeds energy expenditure over a sustained period of time, resulting in the storage of the excess calories in adipose tissue that leads first to an overweight body phenotype (BMI 25 – 30 kg/m^2) and then to the development of a body weight disorder called obesity, defined as a BMI ≥ 30 kg/m^2. Obesity was recently considered a cosmetic problem associated primarily with poor self-control over eating behavior, but is now recognized by the American Medical Association (AMA) as a disease caused by a combination

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Article highlights.

- A large medical need exists for new weight loss therapies, with better efficacy and fewer side effects compared to the anti-obesity drugs currently approved by the FDA.
- Several critical pathways involved in the regulation of energy homeostasis have come from studies of monogenic forms of obesity, for example, the leptin and melanocortin systems.
- GWASs have identified many genetic loci associated with BMI and other obesity-related traits.
- New approaches for modulating the central melanocortin system include AgRP antagonists, MC4R positive allosteric modulators (PAMs), and MC4R chaperones.
- The development of advanced peptide delivery technologies has opened up opportunities to develop new biologics for the treatment of obesity, especially beneficial for high confidence targets that are not amenable to small-molecule drug discovery.
- A new approach for enhancing weight loss efficacy and increasing responder rates is targeted polypharmacology using fixed-dose combinations of two separate drugs (e.g., naltrexone/bupropion) or unimolecular polyagonists, that is, peptides with activities against multiple receptors/enzymes.
- Non-pharmacological approaches involving microbiome replacement therapy or devices may provide viable weight loss options in the future, especially in combination with pharmacological agents.

This box summarizes key points contained in the article.

of behavioral, environmental, and genetic interactions. Excess adiposity is a risk factor for developing co-morbidities such as type 2 diabetes (T2D), cardiovascular disease, and dyslipidemia, all of which can reduce longevity. According to the latest statistics from the United States (US) Center for Disease Control, the prevalence of obesity has rapidly increased over the past decade, with yearly economic costs exceeding $100 billion in the USA alone. With the growth of sedentary lifestyles and Western-style diets throughout the world, especially in developing countries such as China, India, Brazil, and Russia, obesity has become a significant global economic burden [1].

As many biological mechanisms underlie the regulation of energy homeostasis, the treatment of obesity and the subsequent maintenance of lost body weight have proven challenging. Behavioral modifications that promote healthy eating habits and encourage more exercise are recommended as first-line therapy, but often fail to produce sustained, double digit (i.e., > 10%) weight loss due to the adaptive processes that occur to prevent a state of starvation such as a decrease in energy expenditure and an increase in appetite. Pharmacotherapy is used as an adjunct to behavioral changes especially when lifestyle changes fail to produce the desired weight loss, with the choice of drug dependent on the co-morbidities that are present. Bariatric surgery such as Roux-en-Y gastric bypass surgery and several implantable devices such as the adjustable Lap-band®, the Realize® Gastric band, and the Maestro® Rechargeable system are options for morbidly obese patients with BMIs ≥ 40 kg/m^2 or ≥ 35 kg/m^2 with one or more co-morbidities. Bariatric surgery has been shown to produce profound weight loss over 1 year, with some weight re-gain occurring in subsequent years [2-4]. Moreover, bariatric surgery can decrease the risk of developing obesity-related co-morbidities, but carries significant costs and risks that severely restrict its widespread application [5].

Pharmacotherapy for weight loss has evolved considerably over the past decade [6]. A cannabinoid receptor type 1 (CB1R) antagonist, rimonabant, that was approved by the European Medicines Agency (EMEA), but not by the Food and Drug Administration (FDA) was withdrawn in 2009 due to concerns about increased risk of suicidal ideation [7]. An anorectic agent called sibutramine, an inhibitor of neurotransmitter re-uptake, was voluntarily withdrawn in 2010 due to cardiovascular issues, including increased risk of stroke [8]. By 2012, the only weight loss drugs approved for use in the USA were phentermine, an amphetamine derivative that stimulates noreprinephrine release, and orlistat, a pancreatic lipase inhibitor. Phentermine is an anorectic agent that is recommended for short-term weight loss, mostly because of its potential for addiction as a Schedule IV agent (Drug Enforcement Administration classification). It causes side effects such as headache, elevated blood pressure/heart rate, insomnia, dry mouth, and anxiety. Orlistat acts primarily in the gastrointestinal (GI) tract to decrease systemic absorption of ingested dietary fats and is associated with adverse effects such as loose stools [9]. Unlike phentermine, orlistat is approved for use in Europe.

Four new weight loss drugs were approved by the FDA after 2012, providing several new therapeutic options for obese patients in the USA. These drugs have shown varying efficacies and responder success rates in clinical trials (**Table 1**). Lorcaserin (Belviq®) and liraglutide (Saxenda®) are monotherapies that target the 5-HT$_{2c}$ receptor and glucagon-like peptide-1 receptor (GLP-1R), respectively. Phentermine HCl/topiramate extended release (Qsymia®) and naltrexone HCl/bupropion HCl (Contrave™) are fixed-dose combinations with complex polypharmacology [6,10]. Of the four new FDA-approved drugs, only liraglutide and naltrexone/bupropion (Mysimba™) have also been approved as weight loss agents by the EMEA. The placebo-adjusted weight loss of phentermine/topiramate is significantly greater than that for the other approved drugs, presaging a new era of combination approaches for the treatment of obesity [11,12]. These new therapies act primarily at molecular targets in the CNS to decrease appetite. Most FDA-approved weight loss drugs are orally active, with the exception of liraglutide, which requires daily subcutaneous administration.

A large medical need exists for new weight loss drugs, with superior efficacy and improved side-effect profile compared to

Table 1. Weight loss drugs approved in the United States.

Drug	Placebo-adjusted weight loss	Percentage of responding subjects losing > 5% body weight
Orlistat	~ 3%	31% [173,174]
Lorcaserin	~ 3%	25% [173,175]
Liraglutide	~ 4.1%	28% [173,176]
Naltrexone HCl/bupropion HCl	~ 4.5%	25% [173,177]
Phentermine HCl/topiramate extended release	~ 9%	40% [173,178]

the anti-obesity therapies and devices currently approved by the FDA and EMEA. In the past decade, the biological mechanisms underlying the regulation of energy homeostasis have been extensively studied, especially in rodent models, providing many targets that lie at a therapeutic nexus in both essential and ancillary pathways involved in metabolism. Nutrient intake and metabolism are coordinated in part by the hypothalamus, an endocrine organ at the base of the brain. Selected neural pathways such as the leptin-melanocortinergic system in the hypothalamus [13-16] and the adrenergic [17], cannabinoid [18,19], dopaminergic [20], and opioidergic systems [19] in both the hypothalamus and other brain regions are involved in the control of energy homeostasis. Herein, we highlight selected pathways in the CNS that hold particular promise for delivering the next generation of weight loss therapies, focusing on new strategies that engage well-known targets that decrease food intake. Reward pathways that have been implicated in the control of feeding behavior are not included within the scope of this review (the reader is directed to references such as [21] for more information on this subject). We also examine the role of genetic studies in humans in identifying key targets and pathways and discuss recent developments around fixed-dose combinations, targeted polypharmacology, and non-traditional combinations of drugs and devices, which are under investigation in animal models and human clinical studies.

2. Obesity genomics

Numerous twin and family-based genetic studies have established the heritability of obesity, which is estimated to be between 40 and 70% [22]. Cases of severe and mostly early onset monogenic forms of obesity have been shown to arise from mutations in genes in the leptin-melanocortin axis, specifically *LEPR* which encodes the leptin receptor, *POMC* (pro-opiomelanocortin), *PCSK1* (proprotein convertase subtilisin/kexin type 1), *MC4R* (melanocortin-4 receptor), *NTRK2* (tropomyosin receptor kinase B receptor), and *SIM1* (the single-minded 1 transcription factor) [23-25]. Genome-wide association studies (GWASs) have identified additional genetic loci and genes implicated in obesity risk. Until recently, 77 genetic loci were significantly associated with BMI and other obesity-related traits [26-32]. The first susceptibility locus identified for obesity risk, and the common variant with the largest effect size falls in the fat mass and obesity-associated (*FTO)* gene, although the causal variant(s) in the *FTO* locus remains unknown [26]. A landmark study published in 2015 identified 97 BMI-associated loci in a large GWAS and metabochip meta-analysis, which included results from 322,154 and 17,072 subjects of European and non-European descent, respectively [33]. These loci, of which 56 were novel, were shown to account for 2.7% of the variation in BMI and suggest that up to 21% of BMI variation can be accounted for by common genetic variation. Pathway analyses of these loci highlighted the importance of neuronal development, neural plasticity, neural transmission, and various hypothalamic neurocircuitries. Translation of common risk loci for obesity into therapeutic targets can be challenging due to the current limitations of the biological understanding of associated loci and the confounding effects of environmental conditions (i.e., the ubiquitous availability of high-calorie food combined with a sedentary lifestyle), which can interact with genetic predispositions to obesity.

3. Central pathways

3.1 Leptin pathway

Individuals with homozygous loss-of-function mutations in the genes encoding leptin and the leptin receptor (LepR) have normal birth weight but exhibit rapid weight gain in the first few months of life, resulting in severe obesity [34,35]. Leptin, a peptide hormone secreted mainly by white adipose tissue, plays a key role in the control of metabolism [36]. Its ability to suppress food intake, increase energy expenditure, and regulate glucose homeostasis is primarily mediated via engagement of the long isoform of the leptin receptor (LepRb) that is expressed in the hypothalamus [37]. Most obese subjects are hyperleptinemic and fail to respond to exogeneously administered leptin, consistent with a state of leptin resistance [38,39]. The observation that leptin is therapeutically effective for conditions associated with low plasma leptin (e.g., lipodystrophy) supports an inverse relationship between circulating levels and leptin sensitivity [38,40,41]. Reduction of plasma leptin by prolonged caloric restriction during weight loss or by anti-obesity pharmacotherapy (e.g., treatment with exendin-4, a GLP-1R agonist, or pramlintide, an amylin agonist) is associated with improved leptin sensitivity in rodents and humans [42-44]. The use of leptin, alone or in combination with other weight loss agents, has shown potential for the prevention of weight regain [45-47]. A leptin analog, metreleptin, was studied in combination with pramlintide in overweight human subjects first treated for 4 weeks with pramlintide and diet to induce a 2 – 8% weight loss [48]. Following the 4 week lead-in period, the combination therapy

was shown to produce greater weight loss in the weight reduced subjects compared to either metreleptin or pramlintide alone.

Several mechanisms have been proposed to explain leptin resistance. Leptin-induced down-regulation of LepRb may directly contribute to leptin resistance [49]. In this sense, reversing hyperleptinemia may improve hormone responsiveness by favoring re-sensitization of LepRb-mediated responses at specific sites [50,51]. Further studies suggest that constitutive internalization, intracellular retention, and/or slow recycling rate result in low LepRb surface levels under basal conditions [52]. Proteins including endospanin 1 have been shown to retain LepRbs within intracellular compartments [53]. Knockdown of hypothalamic endospanin 1 expression increases LepRb surface levels and reverses diet-induced obesity in mice [54,55]. An innovative phenotypic screen recently identified small molecules that are able to promote both plasma membrane expression and function of LepRbs [56]. The mechanism of action and anti-obesity potential of these compounds remains to be fully defined.

Suppressor of cytokine signaling 3 (SOCS3) and the protein tyrosine phosphatase 1B (PTP1B) are key intracellular factors that negatively control leptin signaling [57]. SOCS3 is up-regulated in response to leptin as part of a negative feedback loop that inhibits LepRb signaling [58]. Given the involvement of both proteins in the development of leptin resistance, pharmacological inhibition of SOCS3 or PTP1B may represent promising approaches to improve leptin responsiveness in obese subjects. Cellular SOCS3 levels can be modified via lentiviral delivery of short hairpin SOCS3 RNA [59]. No peptide or non-peptide modulators of SOCS3 have been reported to date. Several small PTP1B inhibitors have been identified and tested pre-clinically; however the only modulator of the PTP1B pathway in clinical trials is an antisense drug called ISIS-PTP1B$_{RX}$, which was shown to decrease body weight and lower HbA1c in T2D subjects [60-62].

Recent reports suggest that leptin resistance may be associated with defective leptin transport into the brain [63,64]. Shorter leptin receptor isoforms (LepRa,c) have been identified as potential leptin carriers across the blood-brain barrier (BBB) that may be down-regulated with peripheral hyperleptinemia [49,65,66]. The recent discovery that highly specialized cells termed tanycytes regulate hypothalamic leptin uptake may open new avenues to reverse leptin resistance sustained by defective leptin transport [67]. Leptin receptor modulators with improved BBB permeability represent an attractive strategy to circumvent impaired leptin transport mechanisms and engage central LepRs [57,68].

Central leptin resistance may also be induced by hypothalamic endoplasmic reticulum (ER) stress [69]. ER stress suppresses leptin signaling via classical inhibitors of cytokine signaling such as SOCS3 and PTP1B [70]. Pharmacological chaperones that decrease ER stress have been shown to act as leptin-sensitizers and are currently under investigation [41,71].

3.2 Melanocortin system

The central melanocortin system regulates food intake, energy expenditure and overall body weight by modulating complex neuronal pathways/circuits. This system consists of POMC- and agouti-related protein (AgRP)-expressing neurons in the arcuate nucleus (ARC) that integrate information from peripheral energy stores and neural inputs. POMC- and AgRP-expressing neurons secrete anorectic peptides, α- and β-melanocyte-stimulating hormone (α-MSH and β-MSH), and an orexigenic peptide, AgRP, respectively, both of which target downstream neurons expressing the melanocortin-4 receptor (MC4R). MC4Rs expressed in the paraventricular hypothalamus (PVH) control feeding behavior whereas MC4Rs within the dorsal motor nucleus of vagus, lateral hypothalamus, and intermediolateral column regulate other physiological functions such as glucose homeostasis and thermogenesis [72,73].

The endogenous ligands for MC4R, α-MSH in rodents and β-MSH in humans, are derived from proteolytic processing of POMC. α/β-MSH are agonists at MC4R, stimulating adenylate cyclase activity via a Gαs-containing G protein pathway and promoting intracellular accumulation of cyclic adenosine monophosphate (cAMP). AgRP is a competitive MC4R antagonist and an inverse agonist that decreases MC4R constitutive activity on the cAMP pathway. AgRP may not directly compete with α/β-MSH on dendrites, instead acting at distinct sites [74]. Recently, it has been reported that MC4R can signal through Kir7.1 potassium channels in PVH neurons in a G protein-independent manner [75]. The endogenous ligands, α-MSH and AgRP, exhibit opposing effects on the MC4R/Kir7.1 complex, with AgRP causing MC4R to open the Kir7.1 channel, leading to hyperpolarization of neurons.

Mutations in the *MC4R* gene are one of the most common causes of monogenic obesity. Many obesity-linked *MC4R* variants are poorly expressed at the plasma membrane due to misfolding that occurs in the ER. Pharmacological chaperones for MC4R have been shown to increase MC4R cell surface expression, presumably by stabilizing MC4R folding in the ER and decreasing ER-associated degradation. Pharmacological chaperones against *MC4R* mutants provide an exciting disease-modifying opportunity for severe early onset of obesity [76-81].

As acute and reversible activation of POMC neurons has been shown to cause hypophagia, an attractive approach for modulating the melanocortinergic pathway involves direct activation of MC4R using agonists with varying intrinsic activities [82,83]. However, peptidic and non-peptidic MC4R agonists have either failed to significantly decrease body weight in chronic studies in obese human subjects (i.e., NN2-0453, MK-0493) or caused unacceptable cardiovascular side effects (i.e., LY2112688) [82,84-88]. RM-493 is the only MC4R agonist still under active development for obesity as of 2015, with clinical trials ongoing in subjects with a mutation of the *MC4R* gene and subjects with Prader–Willi

syndrome [89]. RM-493 has been reported to increase resting energy expenditure in obese human subjects without stimulating a pressor response [90].

Due to the compelling biology supporting the MC4R pathway in obesity and the human genetics data, several alternative approaches to activating the MC4R system have been investigated. AgRP antagonists potentiate α-MSH activity by selectively blocking AgRP binding to MC4R, but not α-MSH binding [91]. An AgRP antagonist has been advanced into human clinical trials by Transtech Pharma, but data from these studies have not yet been disclosed [92]. MC4R-positive allosteric modulators (PAMs) augment the activity of α/β-MSH at MC4R, thus maintaining the temporal and spatial aspects of endogenous physiological signaling. Vanderbilt University has disclosed small-molecule MC4R PAMs that suppress high-fat diet-induced weight gain in mice [93]. MC4R/Kir7.1-biased agonists that preferentially inhibit MC4R/Kir7.1-mediated potassium flux over MC4R/Gαs-containing G protein activation are hypothesized to decrease food intake without stimulating a pressor response [75]. Clinical efficacy and safety remain to be assessed for new pharmacological approaches targeting MC4R.

Interestingly, MC4R is expressed in the GI tract where it is concentrated in both vagal afferent neurons (VANs) and the basolateral membrane of I and L enteroendocrine cells [94,95]. An MC4R agonist LY2112688 has been found to acutely stimulate total peptide YY (PYY) and GLP-1 secretion in human and mouse *ex vivo* intestinal preparations and in a mouse *in vivo* model [95]. As MC4R expression in the VAN is similar to the LepR, MC4R may play a role in mediating gut peptide signaling from the GI tract to the brain [94]. MC4R agonists have been shown to slow intestinal motility and regulate lipid absorption, in line with a role in promoting negative energy balance [95,96]. A gut-selective MC4R agonist may decrease body weight without the cardiovascular liabilities associated with centrally acting MC4R agonists.

3.3 Opioid pathway

Whereas much focus has been placed on the monogenic forms of obesity linking POMC to MC4R, recent genetic evidence suggests a locus in the mu opioid receptor (MOR) gene *OPRM1* is associated with dietary intake of fat [97]. The endogenous ligand for MOR, β-endorphin, is derived from POMC and secreted by POMC neurons. It acts on pre-synaptic MORs on POMC neurons in the ARC to reduce POMC neuronal activity [98]. β-Endorphin can also be released by POMC neurons in response to CB1R agonists, providing a new mechanism for the physiological regulation of the opioid system [99]. Opioid agonists administered into regions of the brain associated with reward, emotion, and motivation such as the ventral striatum or nucleus accumbens have been shown to: i) increase preferential intake of high-fat/high-sugar-containing foods; ii) increase pleasurable taste reactivity; and iii) enhance motivation to work for a food reward [100-103].

MOR antagonists decrease food intake and body weight in multiple pre-clinical animal models [104,105]. Naltrexone is a non-selective MOR antagonist with kappa opioid receptor partial agonist activity and is efficacious in rodent models of obesity, but not in humans as a weight loss agent [106]. Interestingly, naltrexone can act synergistically with bupropion as a fixed-dose combination to decrease body weight, possibly by increasing POMC neuronal activity [107]. GSK1521498 is a selective MOR antagonist/inverse agonist that was reported to induce a robust weight loss associated with a decrease in the intake of palatable foods in diet-induced obese animals [108]. In a 28-day study in binge-eating obese subjects, GSK1521498 was found to promote a significant reduction in the hedonic responses associated with sweetened dairy products and in the caloric intake of high-fat foods during buffet meals, but was not significantly different from placebo in its effects on body weight, fat mass and binge eating scores [109]. It remains unclear whether opioid receptor subtype selectivity, receptor occupancy, or stratification of the target patient population will increase efficacy and responder rate.

4. Selected signaling pathways with peripheral ligands acting at CNS targets

4.1 GLP-1/GLP-1R

GLP-1 is a pleiotropic enteroendocrine hormone released in response to nutrient intake [110]. Postprandial secretion of GLP-1 results in: i) enhanced insulin secretion; ii) suppression of glucagon secretion; iii) deceleration of gastric emptying; and iv) reduction in food intake. GLP-1 is produced in the periphery by enteroendocrine L cells and in the CNS by preproglucagon neurons in the caudal nucleus of the solitary tract and adjacent medullary reticular formation [111-114]. GLP-1-producing neurons project throughout the brain to many regions involved in energy balance regulation including the hypothalamus. The pharmacological activities of GLP-1 are mediated via the GLP-1R, a class B GPCR that is positively coupled to adenylate cyclase through Gαs-containing G proteins. Neither mutations in genes encoding GLP-1 and GLP-1R nor genetic variants in *Glp1r* support a role for the GLP-1/GLP-1R axis in the regulation of BMI or other body weight traits, although it should be noted that the genetic evidence supporting a link between the GLP-1/GLP-1R axis and T2D is also limited [115].

Peptidic GLP-1R agonists are approved for the treatment of T2D, generally as third-line therapy following metformin and oral medications such as DPPIV inhibitors (**Table 2**). A common side effect observed in clinical trials with these agonists in obese T2D subjects has been weight loss. Liraglutide was investigated as a stand-alone weight loss agent and recently received approval for the treatment of chronic weight management as an adjunct to a reduced calorie diet and exercise, although with a higher starting dose compared to that used in the treatment of T2D (3 vs 1.8 mg, respectively).

Table 2. GLP-1R agonists.

GLP-1R agonists	Originator	Approved indication (unless otherwise indicated)
Liraglutide	Novo Nordisk	T2D, obesity
Exenatide	AstraZeneca	T2D
Lixisenatide	Sanofi	T2D
Albiglutide	GSK	T2D
Dulaglutide	Eli Lilly	T2D
Subcutaneous semaglutide, once weekly	Novo Nordisk	T2D – Phase III
Subcutaneous semaglutide	Novo Nordisk	T2D – Phase II

T2D: Type 2 diabetes.

The weight loss observed in patients taking liraglutide was primarily due to decreased energy intake, not to increased energy expenditure [116]. Several other GLP-1R agonists have demonstrated mixed success in weight loss trials. Dulaglutide was shown to promote similar weight loss in T2D subjects in Phase III clinical trials as comparator GLP-1R agonists whereas once daily oral semaglutide (OG217SC) was found to decrease body weight in Phase II clinical trials in T2D subjects, albeit at dose levels much higher than those used in clinical trials with the weekly subcutaneous (sc) formulation (40 vs 1 mg, respectively) [117,118]. Once weekly subcutaneous semaglutide was shown to decrease body weight in diabetic patients [119]. A once weekly GLP-1R agonist, albiglutide, that is composed of a DPP4-resistant GLP-1-dimer fused to recombinant albumin failed to reduce weight in patients with T2D despite lowering HbA1c by ~ 0.9% [120,121]. Liraglutide has the potential to be first-line therapy for obese T2Ds.

The mechanism of GLP-1R agonist-induced weight loss and decrease in energy intake has been the subject of much investigation. Adverse gastrointestinal events associated with GLP-1R agonists likely contribute to the reduction in food intake as liraglutide-treated patients who experienced at least one episode of nausea or vomiting showed greater weight loss compared to patients who did not experience any such side effects [122]. However, adverse events do not account for all of the body weight loss as many patients that never reported nausea or vomiting still lost weight. Liraglutide was found to increase satiety and fullness, decrease hunger, and slow gastric emptying [116]. The effects on satiety and fullness may be linked to activation of GLP-1Rs in the CNS as radiolabeled liraglutide was detected in the ARC following subcutaneous administration and higher doses of liraglutide were required for effects on food intake compared to glucose lowering, attributed in part to liraglutide's poor CNS penetration [123]. Liraglutide exhibited weight loss efficacy in rats subjected to subdiaphragmatic vagal afferent deafferentation or surgical ablation of the area postrema [123]. Furthermore, electrolytic lesion of PVH neurons and direct injection of exendin (9 – 39), a GLP-1R antagonist, into the ARC were found to impair the ability of liraglutide to reduce body weight in rats, supporting a central mechanism of action [123]. The contribution of neuronal GLP-1Rs in reducing energy intake at clinically efficacious exposures in humans is not known.

4.2 FGF21/FGFR1c/β-Klotho

Modulation of the pathway involving the starvation hormone fibroblast growth factor 21 (FGF21) and its receptor complex FGFR1c/β-klotho has recently emerged as one of the more promising approaches to treat obesity, with several recent studies showing FGF21 and modified analogs, can promote robust weight loss in both rodent and primate models [124-127]. Variants in *FGF21*, while not associated with BMI or obesity, are significantly associated with food preference and macronutrient intake in humans [128,129]. Weight loss in mice treated with FGF21 is due solely to increased energy expenditure via a leptin-dependent mechanism [126]. In contrast, weight loss observed in primates by a modified FGF21 protein derivative known as LY2405319 is primarily mediated via a reduction in food intake, suggesting that the mechanism of action may be different across species [130-132]. In obese T2D subjects, LY2405319 was shown to promote a small decrease in body weight after 28 days (~ 1% placebo-adjusted) [133]. Caloric intake and energy expenditure were not measured, but β-hydroxybutyrate levels were found to be elevated, suggestive of enhanced fatty acid oxidation and a potential increase in total body energy expenditure. A number of biologics that mimic FGF21 or promote binding of β-klotho to FGFR1c have been identified (**Table 3**) [134-138].

The mechanism(s) by which FGF21 modulates body weight across species is not fully understood. Deletion of FGFR1c in the adipose tissue resulted in a significant loss of the effects of FGF21 on body weight in diet-induced obese mice [139]. FGF21 has been shown to cross the BBB and is found in human cerebrospinal fluid (CSF) [140,141]. Intracerebroventricular administration of FGF21 increased the metabolic rate and insulin sensitivity in obese rats [142]. Knockout of β-klotho within the CNS prevented the beneficial effects of FGF21 on body weight in obese mice and abolished FGF21-mediated activation of sympathetic nerve activation to brown adipose tissue [143]. These effects appear to be mediated primarily by the hypothalamus as the metabolic effects of FGF21 were maintained following knockdown of β-klotho expression in the hindbrain [143].

5. Targeted polypharmacology

A new approach for enhancing weight loss efficacy and increasing responder rates is targeted polypharmacology using fixed-dose combinations of two separate drugs (e.g., naltrexone/bupropion) or unimolecular polyagonists, that is, peptides with activities against multiple receptors. Several combinations

Table 3. Drugs in the FGF21/FGFR1c/β-Klotho pathway.

Drug	Originator	Development stage	Ref.
Modified FGF21 protein (LY2405319)	Eli Lilly	Phase I	[135]
Fc-FGF21 fusion peptide	Amgen	Phase I	[179]
Pegylated FGF21 (ARX618)	Ambrx	Phase I	[180]
Antibody linked to FGF21	Pfizer	Phase I	[181]
Agonist antibody (mimAb1)	Amgen	Pre-clinical	[182]
FGFR1c/β-klotho bispecific avimer	Amgen	Pre-clinical	[138]

Table 4. Drug combinations and targeted polypharmacotherapies under investigation.

Drug name	Combination approach	Pharma originator (unless otherwise indicated)	Mechanism
Phentermine/lorcaserin	Fixed-dose combination	Eisai	Sympathomimetic/5-HT2c agonist
Phentermine/ canaglifozin	Fixed-dose combination	Janssen R & D	Sympathomimetic/ SGLT2 inhibitor
RM-493/liraglutide	Fixed-dose combination	Academic study	MC4R agonist/GLP-1R agonist
Oxyntomodulin	Targeted polypharmacology	Academic study	GLP-1R agonist/GCGR agonist
LY2944876	Targeted polypharmacology	Eli Lilly	GLP-1R agonist/GCGR agonist
HM12525A	Targeted polypharmacology	Hammi Pharmaceuticals	GLP-1R agonist/GCGR agonist
ZP2929	Targeted polypharmacology	Zealand Pharmaceuticals/Boehringer Ingelheim	GLP-1R agonist/GCGR agonist
MOD-6031	Targeted polypharmacology	OKPO Health	GLP-1R agonist/GCGR agonist
PSA-oxyntomodulin	Targeted polypharmacology	Xenetic BioSciences/Pharmsynthez OJSC	GLP-1R agonist/GCGR agonist

GCGR: Glucagon receptor; GLP-1R: Glucagon-like peptide-1 receptor; MC4R: Melanocortin-4 receptor;SGLT2: Sodium-glucose cotransporter 2.

of approved anti-obesity monotherapies and investigational drugs are currently undergoing clinical evaluation, for example combinations of sodium-glucose cotransporter 2 (SGLT2) inhibitors with either phentermine or GLP-1R agonists (**Table 4**). Preclinically, combining an MC4R agonist with a GLP-1R agonist has been shown to improve body weight loss and enhance glycemic control in rodent models, with enhanced efficacy compared to MC4R agonist or GLP-1R agonist treatment alone [144]. The superior metabolic efficacy of MC4R agonist/GLP-1R agonist combination therapy has been attributed to the anorectic and glycemic actions of both mechanisms, along with the ability of the MC4R agonist to increase energy expenditure. Interestingly, an increase in mRNA expression for MC4R and GLP-1R was observed with the MC4R agonist/GLP-1R agonist combination in a 5-day chronic study, in contrast to MC4R agonist or GLP-1R agonist treatment alone [144].

Oxyntomodulin is a gut peptide that is derived from the same prohormone precursor as GLP-1 and activates both GLP-1R and glucagon receptor (GCGR) (**Table 5**). As an endogenous unimolecular diagonist, oxytomodulin decreases body weight in rodents by GLP-1R-mediated appetite suppression and GCGR-mediated increase in energy expenditure [145]. Subcutaneous administration of oxyntomodulin promoted only a modest 2.5% weight loss in obese individuals after 4 weeks [146]. Several oxyntomodulin analogs are undergoing clinical evaluation (**Table 4**). Demonstration of superiority to injectable GLP-1R agonists in humans will be critical for differentiation within this class.

A new peptide was recently disclosed that exhibits potent agonist activity at three incretin receptors - GLP-1R, GCGR, and gastric inhibitory polypeptide receptor (GIPR) (**Table 5**) [147]. This unimolecular triagonist was shown to decrease plasma glucose levels and promote robust body weight loss in diet-induced obese rodent models, with greater metabolic benefits compared to diagonists with GLP-1R and GCGR activities. The safety and differentiation profile of the incretin triagonist compared to approved injectable GLP-1R agonists remains to be determined.

Table 5. Structures of agents with targeted polypharmacology.

Drug name	Amino acid sequence
Oxyntomodulin	HSQGTFTSDYSKYLDSRRAQDFVQWLMNTKRNRNNIA
GLP-1R/GCGR/GIPR triagonist	QGTFTSDKSKYLDERAAQDFVQWLLDGGPSSGAPPPS-NH_2 (Aib = aminoisobutyric acid) [147]

6. Non-pharmacological approaches

6.1 Microbiome replacement/supplementation

The gut microbiome has been implicated in the pathogenesis of obesity. A genetic association has been found between obesity and a gene, *TLR4,* encoding a receptor activated by lipopolysaccharides produced by the gut microbiome [33,148].

Consumption of a high-fat diet or use of artificial sweeteners can alter the composition and diversity of the gut microbiome [149-151]. From assessments of the gut microbiome across different populations, several bacterial classes were identified that are associated with obesity and that may influence body weight and metabolic function [152]. Attempts to modulate such bacterial populations through dietary addition of fermentable substrates (prebiotics) or specific bacterial species (probiotics) have shown potential for non-pharmacological approaches to improving metabolism [153,154].

Fecal transfer experiments have demonstrated that gut microbiota can directly contribute to metabolic function. Obese individuals with metabolic syndrome exhibited improvements in insulin sensitivity within 6 weeks of inoculation of intestinal microbes from healthy lean individuals [155]. The effects of fecal transfer experiments on weight loss in humans have not yet been evaluated. Preclinically, transfer experiments of human intestinal microbial communities into germ-free mice demonstrated that an "obese" microbiome directly confers greater adiposity to its recipient than a "lean" microbiome [149,156]. Conversely, microbiota transferred from a severely malnourished individual caused weight loss in germ-free recipients [157]. These experiments suggest the presence of a microbial anorectic signal. Seres Health is pioneering Ecobiotic® therapeutics to treat a range of important medical conditions including metabolic diseases based on microbiome biology.

Gut microbiota have been shown to alter the composition of bile acids and branched chain amino acids, compounds which have been primarily linked to alterations in insulin sensitivity [158-161]. Bile acids may impart effects on energy expenditure through modulation of intestinal farnesoid X receptor (FXR) and bile acid receptor (TGR5) signaling mechanisms as well as stimulation of GLP-1 and PYY secretion [162]. Gut microbiota also synthesize various short chain fatty acids, particularly propionate, which may regulate food intake through direct activation of free fatty acid receptor 2 (FFAR2; GPR43)-dependent stimulation of GLP-1 and PYY secretion from colonic L cells [163,164]. Targeted delivery of propionate to the colon in overweight adults has been shown to increase GLP-1 and PYY secretion and acutely reduce food intake acutely. The durability of chronic propionate administration [165,166].

6.2 Devices

Over the last 15 years, non-surgical, minimally invasive technologies have been sought to bridge the gap between pharmacotherapy and bariatric surgery for the treatment of morbid obesity. Many novel gut-related devices have been shown to promote weight loss, control food intake, and reduce hunger by blocking the vagus nerve, stimulating gastric contractions, reducing stomach volume (e.g., by insertion of restrictive intra-gastric balloons), or inducing malabsorption (e.g., via endoluminal sleeves and food removal) [167-169]. Several obesity-related devices have received a certificate required by the European Union for commercialization of medical devices (i.e., CE Mark Certification) due to their effects on excess weight loss in open-label trials. In contrast, less impressive excess weight loss has been observed in randomized double-blind studies comparing device to sham or restrictive diet and exercise [170]. The Maestro® Rechargeable System was recently approved by the FDA, the first such device since 2007 [171]. The ReShape Duo® Integrated Dual Balloon System met its primary endpoints in a randomized, sham-controlled pivotal obesity trial and is seeking FDA approval.

7. Conclusion

A number of current therapies, combination therapies, and non-pharmacological approaches (e.g., surgery, devices, microbiome replacement therapy) are under investigation for the treatment of obesity. Analyses of monogenic forms of obesity and GWASs have identified important genes and genetic loci associated with BMI and other obesity-related traits, providing targets for pharmacological investigation in many critical pathways involved in the regulation of feeding behavior, for example, the leptin-melanocortin axis and opioid systems. Strategies that engage well-known targets within these systems via novel mechanisms may circumvent issues seen with previous drug candidates that failed in the clinic. Some of the more exciting classes of compounds under investigation within these systems include AgRP antagonists, MC4R PAMs, MC4R or LepRb chaperones, and modulators of LepRb surface expression and internalization. The approval of additional pharmacological and non-pharmacological monotherapies for obesity will create greater opportunities

for combination approaches to increase efficacy and responder success rates.

8. Expert opinion

The fields of obesity research and anti-obesity drug discovery have seen many exciting developments over the past few years that include: i) recognition by the AMA that obesity is a disease; ii) approval of two anti-obesity pharmacotherapies by both the FDA and EMEA (i.e., liraglutide and naltrexone/bupropion) and another two drugs only by the FDA (lorcaserin and phentermine/topiramate); and iii) approval of a vagal stimulator device by the FDA. The first-ever clinical practice guideline for obesity drug treatment offers a new tool for health practitioners looking to the latest pharmacotherapy strategies as a means of treating individual patients with obesity [172].

A paradigm shift has occurred in the way pharmaceutical companies approach new treatments for obesity, with the focus shifting from treatments that are efficacious in the general obese population to treatments that are effective in smaller homogeneous sub-populations of obese subjects. The development of advanced peptide delivery technologies has opened up opportunities to develop new biologics against high confidence targets that are not amenable to small-molecule drug discovery. The GLP-1R agonist, liraglutide, is the first non-oral weight loss drug approved specifically for weight loss. Many monotherapies in Phase II clinical trials for obesity (e.g., beloranib, RM-493) and pre-clinical investigational drugs (e.g., FGF21 biologics) require parenteral administration [6].

Obesity is now recognized as a heterogeneous disease, with complex pathophysiology that is not amenable to long-term therapeutic intervention via a single pathway. Monotherapies provide modest overall weight loss, often with < 50% of subjects losing 10% or more weight loss, resulting in the need for effective combinatorial and patient stratification approaches depending on an individual subject's genetic, dietary and lifestyle behaviors. Innovative strategies are emerging to maximize weight loss efficacy and responder success rates such as: i) fixed-dose combinations of generics; ii) combination of new T2D therapies with approved anorectics (e.g., SGLT-2/phentermine); iii) combinations of injectable peptidic agents (e.g., RM-493 and liraglutide); iv) single drugs with targeted polypharmacologies (e.g., GLP-1/glucagon receptor co-agonists); and v) non-traditional combinations of pharmacotherapies with minimally invasive devices.

Advancements in receptor pharmacology and biology within the leptin-melanocortin pathway have led to re-assessments of old targets previously under investigation. Leptin replacement therapy which failed for weight loss is being re-evaluated as an approach for weight maintenance. New insights around LepRb surface expression has led to novel approaches for counteracting leptin resistance. The discovery that MC4R can couple via a non-traditional G protein-independent mechanism within the PVH has created new opportunities to modulate this target in a safe and effective manner.

Functional genomic studies involving innovative methodologies and technologies applied to larger GWAS and rare variant studies are providing targets not previously associated with BMI. Many historical drugs do not have supportive human genetic data but were pursued based on serendipitous findings of weight loss as a side effect to the primary pharmacology, for example, topiramate (anticonvulsant), naltrexone (alcohol/opioid dependence), bupropion (anti-depressant) and GLP-1R agonists (T2D). A challenge around targets identified from GWASs will be advancing the underlying biology sufficiently to discern directionality of the effect and then to rapidly progress first-in-class therapies into the clinic.

The next decade will see a number of new and exciting approaches to treat obesity. The efficacy and safety standards required for FDA approval of anti-obesity drugs are high and as a result, only a few investigational agents will be able to meet the regulatory criteria and advance onto the marketplace. New drugs that do succeed will hopefully be able to combat the growing prevalence of obesity amongst the general population, resulting in decreased co-morbidities such as T2D and lowering costs to the health care system.

Declaration of interest

The authors are all employees of Pfizer, Inc. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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