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Future Pharmacotherapy for Obesity: New Anti-obesity Drugs on the Horizon

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Abstract

Purpose of Review Obesity is a global health crisis with detrimental effects on all organ systems leading to worsening disease state and rising costs of care. Persons with obesity failing lifestyle therapies need to be escalated to appropriate pharmacological treatment modalities, medical devices, and/or bariatric surgery if criteria are met and more aggressive intervention is needed. The progression of severe obesity in the patient population coupled with related co-morbidities necessitates the development of novel therapies for the treatment of obesity. This development is preceded by increased understanding of the underpinnings of energy regulation and neurohormonal pathways involved in energy homeostasis.

Recent Findings Though there are approved anti-obesity drugs available in the USA, newer drugs are now in the pipeline for development given the urgent need. This review focuses on anti-obesity drugs in the pipeline including centrally acting agents (setmelanotide, neuropeptide Y antagonist [velneperit], zonisamide-bupropion [Empatic], cannabinoid type-1 receptor blockers), gut hormones and incretin targets (new glucagon-like-peptide-1 [GLP-1] analogues [semaglutide and oral equivalents], amylin mimetics [davalintide, dual amylin and calcitonin receptor agonists], dual action GLP-1/glucagon receptor agonists [oxyntomodulin], triple agonists [tri-agonist 1706], peptide YY, leptin analogues [combination pramlintide-metreleptin]), and other novel targets (methionine aminopeptidase 2 inhibitor [beloranib], lipase inhibitor [cetilistat], triple monoamine reuptake inhibitor [tesofensine], fibroblast growth factor 21), including anti-obesity vaccines (ghrelin, somatostatin, adenovirus36).

Summary With these new drugs in development, anti-obesity therapeutics have potential to vastly expand allowing better treatment options and personalized approach to obesity care.

Keywords Anti-obesity drugs · Weight loss medications · Novel targets · Phase 1 and phase 2 trials · Obesity pharmacotherapy · Weight management

Introduction

Obesity causes or exacerbates over 200 medical disorders leading to worsening disease morbidity and mortality [1]. Over one-third of US adults are affected with obesity [2]. Patients with a body mass index (BMI) ≥ 27 with at least one obesity-related comorbidity such as diabetes or hypertension or a BMI ≥ 30 who have failed lifestyle therapies are further recommended for adjuvant anti-obesity pharmacotherapy [3]. There are currently six major Food and Drug Administration (FDA)-approved medications in the USA (Table 1): orlistat [4, 5], phentermine [3, 6], phentermine/topiramate extended-release [7], lorcaserin [8, 9], naltrexone/bupropion sustained-release10, and liraglutide 3.0 mg [10, 11]. Although, in clinical trials, these drugs have a statistically average mean weight loss of 3–7% from baseline [12], the individual weight loss response to these drugs can be variable with some patients losing ≥ 5% initial body weight over 12 weeks and others losing quite less [5, 9, 10, 13–15]. Some patients may also experience adverse effects precipitating the need to abort therapy and try another anti-obesity drug that might have equal efficacy in the individual patient [16]. As a result, it becomes more paramount to explore novel treatment modalities and therapeutics for the treatment of obesity given the urgent need. Thus, this review is timely and

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Table 1 Current major FDA-approved anti-obesity medications

Medication	Approval date in the USA	Contraindications	Warnings and precautions	Side effects
Phentermine	1959	History of cardiovascular disease, concurrent use with monoamine oxidase inhibitors within 14 days, hyperthyroidism, glaucoma, history of drug use, agitated states	Rare cases of primary pulmonary hypertension, increases in heart rate, blood pressure	Insomnia, dry mouth, constipation, agitation
Orlistat	1999	Chronic malabsorption syndrome, cholestasis	Decrease in vitamin absorption; recommend multi-vitamin supplementation with orlistat	Oily spotting, flatus with discharge, diarrhea, fecal urgency
Phentermine/topiramate	2012	Glaucoma, hyperthyroidism, concurrent use with monoamine oxidase inhibitors within 14 days	Fetal toxicity, metabolic acidosis, cognitive impairment	Paraesthesia, dizziness, dysgeusia, insomnia, constipation, and dry mouth
Lorcaserin	2012	Pregnancy	Risk of serotonin syndrome or neuroleptic malignant syndrome-like reactions; discontinue if signs of valvular heart disease develop	In non-diabetic patients: headache, dizziness, fatigue, nausea, dry mouth, and constipation, and in diabetic patients: hypoglycemia, headache, back pain, cough, and fatigue
Naltrexone/bupropion sustained-release	2014	Uncontrolled hypertension, seizures, anorexia nervosa or bulimia, chronic opioid use, concurrent use with monoamine oxidase inhibitors within 14 days	Suicidal behavior and ideation, increase in heart rate and blood pressure, hepatotoxicity, angle-closure glaucoma	Nausea, constipation, headache, vomiting, dizziness, insomnia, dry mouth, and diarrhea
Liraglutide 3.0 mg	2014	Personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia type 2	Thyroid c-cell tumors seen in rats and mice; rarely acute pancreatitis, acute gallbladder disease, renal impairment, increase in heart rate, suicidal ideation and behavior, serious hypoglycemia when used with insulin	Nausea, hypoglycemia, diarrhea, constipation, vomiting, headache, decreased appetite, dyspepsia, fatigue, dizziness, abdominal pain, and increased lipase

All anti-obesity medications are contraindicated in pregnancy

highlights current pharmacotherapeutics for obesity in the pipeline (Table 2) with regard to mechanism of action, safety, and potential clinical utility.

Energy homeostasis involves regulation of caloric intake and energy expenditure [101]. An imbalance or improper regulation or control of homeostasis can cause obesity [101]. Understanding these mechanisms had led to progress in novel pharmacotherapeutics for the treatment of obesity. In the arcuate nucleus of the hypothalamus, two populations of primary neurons respond through afferent and efferent neurohormonal signals derived peripherally and neuronally. Neurons expressing the anorexigenic proopiomelanocortin (*Pomc*) gene release α-, β-, and γ-melanocyte-stimulating hormones (MSHs). MSHs are melanocortin receptor agonists, and central administration of α- or β-MSH (but not γ-MSH), which acts selectively at the MC3R and MC4R, reduces food intake and increases energy expenditure [102, 103]. The second set of primary arcuate neurons expresses the orexigenic gene encoding agouti-related peptide (*AgRP*) [104]. AgRP inhibits POMC activity and functions to increase appetite, reduce satiety, and increase food intake [105]. Targets that either inhibit AgRP activity or stimulate POMC and α-MSH activity either centrally or through peripheral activation via secondary pathways have future potential in the treatment of obesity.

Centrally Acting Agents

Setmelanotide (RM-493, Formerly BIM-22493, IRC-022493)

Our understanding of melanocortin receptor agonists acting in the brain to regulate food intake and satiety and independently affecting insulin sensitivity [106] was advanced by the discovery of POMC mRNA, melanocortin peptides [107], and cloning of the melanocortin receptors in 1992 [108]. It is now well known that mutations in the *MC4R* gene leading to energy dysregulation cause monogenic obesity [17] as exemplified in the Pima Indian population [109] noted to have a high prevalence of *MC4R* loss-of-function variants, associated with obesity, type 2 diabetes mellitus, and lower resting energy expenditure.

Table 2 New anti-obesity drugs under investigation

Drug	Alternative names	Mechanism of action	Potential effects as seen in either animal or human studies	Side effects or concerns	Clinical benefits	Reference
Centrally acting agents						
Setmelanotide	RM-493, formerly BIM-22493, IRC-022493	MC4R-agonist target	Decrease in body weight and increase in energy expenditure	Headaches, arthralgia, nausea, spontaneous penile erections, and female genital sensitivity	Currently being evaluated for rare genetic disorders	[17–19]
Velneperit	S-2367	Neuropeptide Y5 receptor antagonist	Anorexia	Discontinued from development after little weight loss (3.8 vs 0.8 kg placebo) in phase 2 clinical trials	Successful proof-of-concept study	[20–22]
Zonisamide-bupropion	Empatic	Antiepileptic agent with properties of sodium channel modulation, carbonic anhydrate inhibition, dopamine and serotonin transmission combined with a dopaminergic agent	Greater weight loss than monotherapy alone; zonisamide-induced depression and sedation effects with its anti-seizure properties complement to seizure-inducing anti-depressive effects of bupropion	Nausea, headache, insomnia	Phase II trials completed	[23, 24]
Cannabinoid type-1 receptor blockers	SR141716, AM251, AM 6545	Antagonism of cannabinoid type-1 receptors stimulates anorexigenic signaling	Weight loss in animal studies	Older compounds had centrally mediating effects leading to depression and mood alterations	Peripheral antagonist AM6545 with limited CNS penetration under exploration	[25–33]
Gut hormones and incretin effects						
Semaglutide	NN9536; oral GLP-1 agonists: semaglutide, TTP054/TTP-054 and ZYOGI	Glucagon-like-1 receptor (GLP-1) agonists	Significant reductions in A1c, weight loss	Fewer hypoglycemic events, safety profile similar to other GLP-1 agonist	Type 2 diabetes mellitus, obesity	[34–37]
Amylin mimetics	Davalintide (AC2307), KBP-088, KP-042 (dual amylin and calcitonin receptor agonists)	Pancreatic B-cell hormone which acts as a centrally acting satiety signal, reducing food intake, slowing gastric emptying, and reducing postprandial glucagon secretion; human amylin receptor subtypes are complexes of calcitonin receptor	Reduces food intake and body weight, improvement of oral glucose tolerance	Hypoglycemia	Type 2 diabetes mellitus, obesity	[38–46]
Glucose-dependent insulinotropic polypeptide (GIP) analogue	ZP4165	Increased GIP signaling in adipose tissue induced insulin resistance, lipid storage and hepatic steatosis; combination GLP-1 agonist and GIP and enhance GLP-1 induced weight loss	Insulinotropic effects and reduced A1c levels in diabetic mice; no effect on weight loss		Type 2 diabetes mellitus, obesity	[47]
Dual action GLP-1/glucagon receptor antagonist	Oxyntomodulin, MED10382, G530S (glucagon analogue + semaglutide), GC-co-agonist 1177	Though glucagon monotherapy causes hyperglycemic effect, combination GLP-1 agonist and glucagon was noted to induce anorexia in studies	Appetite suppression, reduction of food intake, and increase in energy expenditure	Effects are short-lived limited clinical utility	Glucagon analogues with longer half-lives are in development	[48–51]

Table 2 (continued)

Drug	Alternative names	Mechanism of action	Potential effects as seen in either animal or human studies	Side effects or concerns	Clinical benefits	Reference
Triple agonist	Tri-agonist 1706	Combination glucagon-GIP-GLP-1 agonist			Under development	[52]
Peptide YY	PYY	Anorexigenic peptide which decreases gastric motility, increases satiety, and inhibits NPY receptors	Reduces appetite and decreases food intake	Short-acting half-life and stability limit clinical utility	PYY infusion has been shown to reduce orexigenic hormone ghrelin levels. Lower PYY levels with a blunted rise in PYY postprandially in obesity	[53–60]
Leptin analogues	Metreleptin (Myalept)	Human recombinant leptin injectable analogue	Improves hyperglycemia, hypertriglyceridemia, decreases hepatic fatty steatosis	Previous indication for hypothalamic amenorrhea has been discontinued. Most common adverse effects in clinical trials includes headaches, hypoglycemia, decreased weight and abdominal pain	Approved in Japan for lipodystrophic disorders and approved in USA for non-HIV generalized lipodystrophy	[61–68]
	Pramlintide-metreleptin	Synthetic analogue of amylin peptide combined with leptin analog; pramlintide is approved for treatment of type 1 or 2 diabetes	Average weight loss 11% in clinical trials on combination, reduction of food intake	Mild to moderate nausea	Diabetes, obesity	[22, 69–72]
Other novel targets						
Beloranib		Fumagillin analogue with methionine aminopeptidase 2 inhibition acting to reduce new fatty acid molecules by the liver and converting stored fats into useful energy; originally designed as an angiogenesis inhibitor	Can cause robust weight loss and hypophagia in rat models of hypothalamic and genetic obesity; weight loss, improvements in lipids, C-reactive protein, adiponectin	Sleep disturbance and gastrointestinal side effects	Phase III trial aborted in December 2015 after 2nd reported patient death in Prader-Willi trial	[73–79]
Lipase inhibitor	Cetilistat (ATL-962)	Pancreatic and gastric lipase inhibitor	Weight loss and improvements in lipid profile	Gastrointestinal side effects better tolerated than orlistat	Obesity, hyperlipidemia, prediabetes, diabetes	[80–82]
Triple monoamine reuptake inhibitor	Tesofensine	Triple monoamine reuptake inhibitor of dopamine, norepinephrine, and serotonin	Weight loss with increases in forebrain dopamine levels in animal studies; mean weight reduction of 4.5–10.6% in clinical trials	Pharmacological similar to sibutramine and has potential to increase heart rate, blood pressure and psychiatric disorders	Further studies to assess safety are needed	[83–85]
Fibroblast growth factor	FGF21	Fibroblast growth factor family that functions as metabolic regulator with beneficial effects on both weight loss and improved glycemic control	Stimulation of glucose uptake, adiponectin secretion with browning in susceptible white adipose tissue depots; thermogenesis and increase in energy expenditure; regulation of fatty acid oxidation and lipid homeostasis in liver	Obesity state is FGF21-resistant, thus limiting clinical utility	Further studies are needed	[86–92]

Table 2 (continued)

Drug	Alternative names	Mechanism of action	Potential effects as seen in either animal or human studies	Side effects or concerns	Clinical benefits	Reference
Anti-obesity vaccines (proof-of-concept studies)	Ghrelin	Orexigenic hormone secreted by fundus cells of the stomach	Decrease in food intake, decrease hypothalamic orexigenic signals, and increase energy expenditure in animal studies	No weight loss seen in human clinical trials of the vaccine		[93–95]
	Somatostatin	Peptide hormone which inhibits growth hormone and insulin-like growth factor 1 secretion (IGF-1)	Reduced GH secretion has been associated with obesity and increased adiposity; somatostatin vaccination might remove inhibitory effects of somatostatin and increase endogenous levels of GH and IGF-1	In animal studies, vaccination did not affect changes in food intake		[96, 97]
	Adenovirus36 (Ad36)	Ad36 is associated with obesity, inflammation and increased adiposity	In animal studies, vaccinated mice had greater reduction in body weight and decreased inflammatory changes in fat tissue			[98–100]

In comparison, the *MC3R* gene has a more crucial role in foraging behaviors and maintenance of energy homeostasis during nutrient scarcity [110].

Setmelanotide is a novel synthetic MC4R-agonist target shown to decrease body weight and increase energy expenditure in non-human primates [18, 19]. In a randomized, double-blind, placebo-controlled, crossover study [17], the effects of setmelanotide (1 mg/24 h by continuous subcutaneous infusion over 72 h) were examined on resting energy expenditure (REE) in patients with obesity (six men and six women with BMI 35.7 ± 2.9 kg/m^2 [mean ± SD]) studied in an inpatient setting in conjunction with a weight-maintenance diet and 30 min of daily exercise. Patients had increased REE compared to placebo by 6.4% (95% confidence interval, 0.68–13.02%), with higher total daily EE and lower respiratory quotient (0.833 ± 0.021 vs 0.848 ± 0.022; $p = 0.02$). No adverse effect on heart rate or blood pressure was observed.

Setmelanotide treatment was associated with small increases in plasma fasting glucose, insulin, C-peptide, triglyceride, FFA, and total GLP-1 and PYY levels in a crossover study [17]. Though MC4R agonists have been previously reported to increase BP and heart rate [111], no adverse effects on heart rate or blood pressure were noted. Other mild, transient side effects included headache, arthralgia, nausea, spontaneous penile erections, and female genital sensitivity [17]. Setmelanotide is currently being evaluated for the following rare genetic disorders of obesity: POMC deficiency obesity, LepR deficiency obesity, Prader-Willi syndrome, Bardet-Biedl syndrome, Alström syndrome, POMC heterozygous deficiency obesity, and POMC epigenetic disorders [112–114]. Setmelanotide has the potential for replacement therapies for MC4R pathway deficiencies found in rare genetic disorders of obesity.

Neuropeptide Y Antagonists (Velneperit [S-2367])

Velneperit (S-2367) is an Y5 receptor antagonist that prevents binding of NPY to Y5 receptors, thus decreasing hunger and increasing satiety. It was originally developed by Shionogi as a possible obesity drug due to its anorectic effects, but was discontinued from further development after disappointing results showing modest weight loss in phase II clinical trials [20, 21]. The trials [22] enrolled 1566 patients with obesity and evaluated efficacy and safety of two doses (800 and 1600 mg) vs placebo, in combination with either a reduced-calorie diet (RCD) or a low-calorie diet (LCD). Patients receiving 800 mg lost an average of 3.8 kg compared to placebo (0.8 kg; $p < 0.0001$) with 35% of patients losing > 5% of their initial body weight (placebo 12%). The 54-week LCD study with 1600-mg dose showed a weight loss of 7.1 vs 4.3 kg in placebo with 52% of the patients in the treatment group losing > 5% of initial body weight (placebo 35%). Preliminary data from the study showed that velneperit met primary end points of weight reduction and secondary end points of improvements in lipid profile and reduction of weight circumference. However, it was still considered a

successful proof-of-concept of the potential of Y5 receptor antagonists as possible anti-obesity agents in the future. Combination of velneperit and orlistat is also being explored in clinical trials by Shionogi [115].

Zonisamide-Bupropion Slow-Release [Empatic]

The combination drug zonisamide-bupropion (Empatic) has been shown to induce weight loss in clinical trials [23, 24]. Zonisamide is an antiepileptic agent with properties of sodium channel modulation, carbonic anhydrase inhibition, and dopamine and serotonin transmission, used to treat partial seizures with known weight loss as a side effect. Bupropion, a dopaminergic agent, approved for the treatment of depression and smoking cessation, also decreases appetite and has been linked to weight loss as monotherapy. The zonisamide-induced depression and sedation effects coupled with its anti-seizure properties complement well to the seizure-inducing anti-depressive effects of bupropion [22, 116]. The combination was found to be superior to monotherapy in a small pilot study involving 18 women with obesity [23]. The combination zonisamide (initially given at a dose of 100 mg and then titrated to 400 mg by 4 weeks) plus bupropion (100-mg immediate release, titrated to 200 mg after 2 weeks) had an average weight loss of − 7.2 kg (7.5%) at 12 weeks compared to placebo (2.9 kg, 3.1%). The zonisamide monotherapy group had a 44% dropout rate due to poor tolerance and side effects, compared to 22% in the combination treatment group. In a 24-week phase IIb double-blind, placebo-controlled trial [24] of Empatic in 729 patients with obesity (BMI 27–45 kg/m^2), patients in the treatment arm had greater weight loss (bupropion 360 mg + 120 mg zonisamide dosage − 6.1%; bupropion 360 mg + 360 mg zonisamide − 7.5%) compared to placebo (1.4%) and monotherapy with zonisamide (3.2% on 120 mg and 5.3% 360 mg) and bupropion 360 mg (2.3%). In the buproprion 360 mg + 120 mg zonisamide group, 46.9% of patients lost > 5% of initial bodyweight and 60.4% in the buproprion 360 mg + zonisamide 360 mg group. Nausea, headache, and insomnia were the most common reported adverse events. Cognitive impairment, depression, anxiety, and suicidal ideation were not statistically different between placebo and Empatic groups. Empatic has completed phase II trials [116].

Cannabinoid Type-1 Receptor Blockers (SR141716, AM251, AM6545)

Activation of cannabinoid type-1 (CB1) receptors) [25] by cannabinoids stimulates orexigenic signaling while antagonism of CB1 receptors stimulates anorexigenic signaling leading to inhibition of food intake [26, 27]. Previous older targets including CB1 receptor antagonist/inverse agonist SR141716 rimonabant [28, 29] and AM251 [30] were shown to promote weight loss in animal studies. However, these older CB1 therapeutic antagonist targets had potential for centrally mediating effects. More specifically, rimonabant caused depressive disorders or mood alterations in up to 10% of patients and approximately 1% suicidal ideation rates. Furthermore, nausea and upper respiratory infections were quite common in > 10% of patients with other reported adverse effects ranging from gastroenteritis, anxiety, irritability, insomnia, sleep disorders, hot flushes, diarrhea, vomiting, dry or itchy skin, tendonitis, muscle cramps and spasms, fatigue, to flu-like symptoms, and increased risk of falling [31]. Clinical trials and postmarketing surveillance data showed that the risk of psychiatric disorders including depressed mood disorders, anxiety, and suicidal ideation in people taking rimonabant was doubled, and thus, it was withdrawn from the market in 2009 [32, 33]. Regardless, these earlier studies served as proof-of-concept that cannabinoid antagonists may be useful targets with anti-obesity effects. A novel peripheral cannabinoid antagonist (AM6545) with limited CNS penetration is under exploration. In animal studies, it inhibited food intake and body weight gain without aversive side effects [117, 118].

Gut Hormones and Incretin Effects

Semaglutide (NN9536) and Oral GLP-1 Agonists (Semaglutide, TTP054/TTP-054 and ZYOG1)

Glucagon-like-peptite-1 [GLP-1] receptors are also found directly on the brain and act through a diverse neural circuitry involving peripheral GLP-1 signaling to control food intake and body weight regulation [119]. Liraglutide 3.0 mg once-daily subcutaneous injection, a GLP-1 analogue, is available and currently approved for the treatment of obesity. It has shown efficacy in patients with obesity and type 2 diabetes [10, 11]. However, there are no present extended-release formulations of GLP-1 approved for the treatment of obesity. Semaglutide is a long-acting GLP-1 analogue in the pipeline for both obesity (phase 2) and type 2 diabetes mellitus (phase 3) that shows promise. In a randomized, double-blind, placebo-controlled, two-period crossover trial investigating the effects of 12 weeks of treatment with once-weekly subcutaneous semaglutide, dose-escalated to 1.0 mg in 30 patients with obesity compared to placebo, semaglutide resulted in 24% reduction in total energy intake across all ad libitum meals per day ($p < 0.0001$) and a − 5.0-kg reduction from baseline body weight with improved cravings and better control of eating [34].

The safety and efficacy of once-weekly semaglutide for the treatment of type 2 diabetes has been evaluated in several trials [35–37]. Semaglutide has resulted in greater reductions in HbA1c and weight, with fewer hypoglycemic events. Semaglutide has been well tolerated, with a safety profile similar to that of other GLP-1 receptor agonists. Though most common side effects on GLP-1 receptor agonists include nausea and bloating, data from randomized controlled trials indicate that the incidence of pancreatitis and pancreatic cancer with GLP-1 is not significantly different from that observed in placebo/non-

GLP-1 drugs (HR < 1, $p > 0.05$), whereas a statistically increased risk of cholelithiasis (OR [95% CI] 1.30 [1.01–1.68], $p = 0.041$) warrants attention [120]. The GLP-1 agonist-induced thyroid C-cell hyperplasia seen in rodents may not be applicable to humans [121]. Semaglutide will most likely be beneficial in patients with type 2 diabetes mellitus, prediabetes, or insulin resistance and in those patients who would prefer not to take daily injections. The safety profile is similar to other GLP-1 agonists currently available and being prescribed such as liraglutide 3.0 mg subcutaneously for the treatment of obesity.

Furthermore, investigational oral semaglutide for type 2 diabetes mellitus is currently in phase 3 trials [52]. In the phase 2 dose-finding study, HbA1c and weight reduction were of similar magnitude to those seen with the injectable GLP-1 receptor agonist formulations, and there were no red flags in terms of safety. Because food can interfere with oral semaglutide absorption, the drug was given fasting at least 30 min before meals in the morning [122]. Other oral small-molecule GLP-1 agonists, such as TTP054/TTP-054 and ZYOG1 with attractive alternative to injectable agents while retaining efficacy of GLP-1 agonist and minimizing adverse effects, are being studied [123].

Amylin Mimetics (Davalintide [AC2307] and KBP-088, KP-042 [Dual Amylin and Calcitonin Receptor Agonists [DACRA])

Amylin, a pancreatic B-cell hormone, acts as a centrally acting satiety signal, reducing food intake, slowing gastric emptying, and reducing postprandial glucagon secretion by exerting an effect through the area postrema where peripheral peptide signaling can have direct connection to the brain neurons and the central nervous system from the blood-brain barrier [38]. The area postrema also connects to the nucleus of the solitary tract and other autonomic control centers in the brain [39]. Subsequently, the amylin signal exerts a control over energy pathways by decreasing the expression of orexigenic neuropeptides [38]. The human amylin receptor subtypes are complexes of the calcitonin receptor with receptor activity-modifying proteins [40]. Because of their mechanism of action, amylin mimetics coupled with calcitonin receptor agonists known as dual action amylin and calcitonin receptor agonists (DACRA) are novel anti-obesity drug discovery targets of study.

Davalintide (AC2307), an amylin-mimetic peptide, has demonstrated in animal studies to reduce food intake and body weight with enhanced metabolic activity over amylin [41, 42]. In more recent studies, DACRA KBP-088 has shown superiority over davalintide with regard to in vitro receptor pharmacology and in vivo efficacy of food intake and body weight [43]. Moreover, DACRA KBP-088 and KBP-042 improved oral glucose tolerance and alleviated hyperinsulinemia with sustained weight loss effects and reduction in adipocyte hypertrophy in high-fat diet-fed rats [43–46]. A long-acting amylin analogue intended as a once-daily treatment is also in phase 1 of investigation product development [52].

Glucose-Dependent Insulinotropic Polypeptide (GIP) Analogue (ZP4165)

GIP, originally named "gastric inhibitory peptide," is a 42-amino-acid polypeptide hormone isolated from porcine intestine K-cells that inhibited gastric secretion in dogs but subsequent human studies could not confirm inhibition of gastric secretion [124]. Later research demonstrated a glucose-dependent insulinotropic effect, suggesting an incretin role. GIP acts to stabilize blood glucose levels with inverse glucose-dependent effects on pancreatic insulin and glucagon secretion, respectively [125]. Extrapancreatic effects also include anabolic bone properties where GIP inhibits bone resorption of osteoclasts and stimulates bone formation of osteoblasts [126]. GIP has a role in lipid metabolism (receptors found on adipocytes) with lipids further promoting GIP secretion [127–129]. Increased GIP signaling in adipose tissue induces insulin resistance, lipid storage, and hepatic steatosis and has been implicated in visceral fat accumulation [130]. Thus, high GIP levels can cause the development of obesity and insulin resistance with the inverse effect through inhibition [131]. In animal studies [47], though the GIP analogue ZP4165 demonstrated insulinotropic action in rats and also reduced hemoglobin A1c levels in diabetic mice, similar to the GLP-1 agonist, it did not alter body weight of obese mice. It did, however, enhance GLP-1-induced weight loss, suggesting that combination GIP and GLP-1 agonist warrants further exploration for obesity and diabetes treatment, rather than monotherapy with GIP.

Dual Action GLP-1/Glucagon Receptor Agonists (Oxyntomodulin, MEDI0382, G530S [Glucagon Analogue + Semaglutide], GC-Co-agonist 1177) and Triple Agonist Glucagon-GIP-GLP-1 Agonist (Tri-agonist 1706)

Glucagon is a peptide hormone secreted by the α-cells of the pancreas. It is a catabolic hormone involved in raising blood glucose through glycogen breakdown and glucose release by hepatocytes [132, 133]. It was first noted to reduce food intake in humans over 50 years ago, likely related to its effects on decreasing meal size and increasing satiety [134]. Subsequent research exploring co-administration of GLP-1 agonist and glucagon noted an anorectic effect with neuronal activation in the area postrema and central nucleus of the amygdala in contrast to the hyperglycemic effect of glucagon monotherapy [48].

Oxyntomodulin is an endogenous 37-amino-acid peptide that contains the 29-amino-acid sequence of glucagon followed by an 8-amino-acid carboxyterminal extension. It is a natural GLP-1/glucagon dual receptor agonist peptide produced by the endocrine enteral L-cell cells, and is known to suppress appetite, decrease food intake, and increase energy expenditure [49, 50].

It has shown to reduce bodyweight by 2.3 ± 0.4 kg in the treatment group over the study period compared with 0.5 ± 0.5 kg in the control group ($p = 0.0106$) following 4 weeks of treatment in persons with overweight and obesity [51]. However, oxyntomodulin's effects are short-lived, limiting its clinical application and thus synthetic novel dual action analogues with longer half-lives, such as MEDI0382 [135], G530S [glucagon analogue + semaglutide] [52], and GC-co-agonist 1177 [52], are being evaluated in animal models. A triple glucogon-GIP-GLP-1 agonist (tri-agonist 1706) [52] is also being developed.

Peptide YY (PYY)

PYY is a 36-amino-acid anorexigenic peptide with a hairpin-like U-shaped fold secreted from the entero-endocrine L cells of the ileum and colon in response to feeding [53, 54]. Although PYY exists in two major forms, PYY1-36 and PYY3-36, the most common form of circulating biologically active PYY is PYY3-36, which binds to the Y2 receptor (Y2R) of the Y family of receptors and shares a structural homology to NPY and pancreatic polypeptide [54]. PYY functions to reduce appetite and decrease food intake [55] by decreasing gastric motility, increasing satiety, and inhibiting NPY receptors [56]. Persons with obesity not only have lower PYY levels but the rise in PYY is blunted postprandially though both lean and obesity subjects experience reduced hunger and caloric intake [55]. PYY infusion has also been shown to reduce the orexigenic hormone ghrelin levels [55]. High protein intake has been shown to increase both GLP-1 and PYY release [57]. Failure to sustain elevated PYY levels has also been implicated in weight regain post-bariatric surgery [58]. Though PYY is an attractive therapeutic anti-obesity drug to study, there have been several limitations, primarily its short half-life affecting clinical utility and stability [59]. Various approaches are being trialed in phase 1 and II investigations including developing long-acting subcutaneously administered analogues, oral and intravenous formulations, and nasal sprays [60].

Leptin Analogues (Metreleptin [MYALEPT], Combination Pramlintide-Metreleptin)

Leptin, a hormone produced by adipocytes, was initially thought to be a successful treatment for obesity as early animal studies linked leptin deficiency to severe obesity. However, on the contrary, persons with obesity are leptin-resistant and have higher levels of leptin [136]. Thus, mechanisms to overcome leptin resistance using combination therapy are currently being explored.

Metreleptin (Myalept), an injectable human recombinant leptin analogue which improves hyperglycemia and hypertriglyceridemia and decreases hepatic fatty steatosis, has demonstrated a role in lipodstrophic disorders characterized by congenital or acquired loss of adipose tissue, in both children and adults [61–64]. It is approved in Japan for metabolic disorders including lipodystrophy and in the USA in 2014 as the first and only treatment of patients with non-HIV-related forms of generalized lipodystrophy such as leptin deficiency and congenital or acquired lipodystrophy [65]. Previous indication for hypothalamic amenorrhea has been discontinued [66]. Development of antimetreleptin antibody immunogenicity might occur and has been implicated in possible weight regain or loss of efficacy associated with metreleptin treatment [67]. The drug is thus contraindicated in patients with general obesity not associated with congenital leptin deficiency due to lack of efficacy in this target population and immunogenicity with neutralizing activity reported in patients with obesity treated with metreleptin. T-cell lymphoma has been reported in patients with acquired generalized lipodystrophy regardless of treatment with metreleptin. Most common adverse reported side effects in clinical trials (≥ 10%) were headaches, hypoglycemia, decreased weight, and abdominal pain [68].

Pramlintide, a synthetic analogue of amylin peptide hormone with glucose regulatory and anorexigenic actions secreted in response to food intake, has been shown to reduce food intake and body weight [69]. It is currently approved for the treatment of type 1 or 2 diabetes, though it reduces food intake and body weight in persons with obesity regardless of diabetes status [70]. Pramlintide is a short-term satiety signal whereas leptin is a long-term adiposity signal. Animal models pre-treated with pramlintide showed improvement of leptin signaling, suggesting a synergistic or additive effect of the neurohormonal combination [71]. In a 24-week, randomized, double-blind, active-drug-controlled, proof-of-concept study in 177 persons with overweight and obesity, combination treatment with pramlintide/metreleptin led to greater weight loss from enrollment to week 20 (− 12.7 ± 0.9%) than treatment with pramlintide (− 8.4 ± 0.9%; $p < 0.001$) or metreleptin (− 8.2 ± 1.3%; $p < 0.01$) alone, with weight loss continuing without evidence of a plateau [72]. Most common side effects were mild to moderate nausea which decreased over time. Based on these significant findings, a phase 2b trial of pramlintide + metreleptin was completed in late 2009 with an extension of the study up to 52 weeks [22]. The phase 2b 28-week, double-blind, placebo-controlled study enrolled 608 subjects with overweight or obesity randomized to various dosages of pramlintide, pramlintide + metreleptin, or placebo. At the completion of the study, subjects with baseline BMI < 35 kg/m^2 on the highest dosage of pramlintide + metreleptin had an average weight loss of 11% ($p < 0.01$; placebo 1.8%; monotherapy groups ~ 5%). Furthermore, in the 52-week extension of the study, subjects in the treatment group showed sustained weight loss, whereas the placebo arm regained almost all the weight [22].

Other Novel Targets

Beloranib

Beloranib is an analogue of the natural chemical compound fumagillin and is a methionine aminopeptidase 2 (MetAP2)

inhibitor acting to reduce production of new fatty acid molecules by the liver and converting stored fats into useful energy [73]. Originally designed as an angiogenesis inhibitor for the treatment of cancer, clinical focus shifted to anti-obesity therapeutics once potential effects of MetAP2 were realized [74, 75]. In an ascending dose-trial of beloranib in 31 women with obesity randomized to intravenous 0.1, 0.3, or 0.9 mg/m^2 beloranib or placebo twice weekly for 4 weeks, median weight loss with 0.9 mg/m^2 beloranib was − 3.8 kg (95% CI − 5.1, − 0.9; $N = 8$) versus − 0.6 kg with placebo (− 4.5, − 0.1; $N = 6$) [76]. The drug was also noted to show improvements in lipids, C-reactive protein, and adiponectin. The efficacy, safety, and tolerability of the drug was assessed in a phase 2, double-blinded, randomized study investigating the effects of beloranib suspension (0.6, 1.2, 2.4 mg) or placebo, administered subcutaneously for 12 weeks in 147 participants with obesity [77]. At week 12, beloranib resulted in dose-dependent progressive weight loss of − 5.5 ± 0.5, − 6.9 ± 0.6, and − 10.9 ± 1.1 kg for the 0.6-, 1.2-, and 2.4-mg beloranib doses, respectively, compared with − 0.4 ± 0.4 kg with placebo (all $p < 0.0001$ vs placebo) with corresponding improvements in cardiometabolic risk factors. The drug appeared safe and well tolerated with sleep disturbance and gastrointestinal adverse effects most commonly reported. Beloranib has also been implicated to cause robust weight loss and hypophagia in rat models of hypothalamic and genetic obesity [78]. In December 2015, phase III beloranib clinical trials for Prader-Willi were discontinued after a second patient death and obstacles to getting FDA approval for the drug [79].

Lipase Inhibitor (Cetilistat [ATL-962])

Cetilistat [ATL-962] is similar to the older drug orlistat (xenical) and acts as a pancreatic and gastric lipase inhibitor. In diet-induced obesity rats, the drug ameliorated body weight gain and caused improvements in lipid profiles [80]. In a phase 2, multicenter, randomized, placebo-controlled, parallel group study, patients ($n = 371$ who met entry criteria) were randomized to either placebo or one of three different doses of cetilistat (60 mg three times daily, 120 mg three times daily, or 240 mg three times daily) for 12 weeks, followed by a 4-week post-treatment follow-up [81]. Cetilistat group had statistically significant mean body weight reductions compared to placebo (60 mg—3.3 kg, $p < 0.03$; 120 mg—3.5 kg, $p = 0.02$; 240 mg—4.1 kg, $p < 0.001$) with improvements in lipid profile at all the dosages. Treatment-emergent adverse events were similar between the groups, with the cetilistat group having greater gastrointestinal adverse events (1.8–2.8% of subjects in the treatment group). In another phase 2 trial comparing cetilistat to orlistat vs placebo, cetilistat was found to be well tolerated and showed fewer discontinuations due to adverse effects than in the placebo and orlistat groups [82]. The significant reductions in body weight with improvement of glycemic control in patients with type 2 diabetes and obesity compared to placebo were similar for both orlistat and cetilistat. Thus, the drug shows promise over orlistat while alleviating potential negative gastrointestinal side effects such as diarrhea, flatulence, and oily spotting [82].

Triple Monoamine Reuptake Inhibitors (Tesofensine [TE])

Tesofensine (TE) is a novel triple monoamine potent reuptake inhibitor of neurotransmitters dopamine, norepinephrine, and serotonin. In animal studies, TE produced weight loss with increases in forebrain dopamine levels in diet-induced obesity rats, suggesting that its effects could be interrelated to central dopaminergic activity [83]. In phase 2 trial of 203 persons with obesity randomized to treatment with TE 0.25, 0.5, or 1.0 mg, or placebo daily for 24 weeks, TE treatment resulted in a mean weight reduction of 4.5, 9.2, and 10.6% higher than that of placebo for 0.25, 0.5, and 1.0 mg, respectively ($p < 0.0001$) [84]. Though TE showed robust anti-obesity effects in clinical trials, further studies to assess safety and efficacy of TE are needed. TE shares pharmacological properties with sibutramine and has potential to increase heart rate, blood pressure, and psychiatric disorders [85].

Fibroblast Growth Factor (FGF21)

Fibroblast growth factor (FGF) 21, expressed primarily in the liver, but also found in adipose tissue, skeletal muscle, and pancreas, is a member for the FGF family that functions as a metabolic regulator with beneficial effects of both weight loss and improved glycemic control [86]. The molecule functions on multiple target organs and acts as a tri autocrine, paracrine, and endocrine factor. In white adipose tissue, FGF21 stimulates glucose uptake and adiponectin secretion with browning in susceptible white adipose tissue depots. In brown adipose tissue, FGF21 also stimulates both glucose uptake and thermogenesis. The ability to increase energy expenditure makes it an exciting target for the study of anti-obesity drugs. In the liver, FGF21 inhibits growth hormone signaling; regulates fatty acid oxidation both in fasted state and in mice consuming high-fat, low-carbohydrate ketogenic diet; and maintains lipid homeostasis [87–90]. The molecule also possesses anti-inflammatory anti-oxidative stress properties with its circulating concentration increasing during periods of muscle-related or critical stress [91]. Though an attractive novel anti-obesity and anti-diabetes target of study, FGF21 levels are elevated in obese ob/ob and db/db mice and correlate positively with BMI in humans while exogenous dosages of FGF21 in diet-induced mice show virtually absent beneficial effects on glucose tolerance and lipid metabolism, suggesting that the obesity state is FGF21-resistant [92].

Anti-obesity Vaccines (Ghrelin, Somatostatin, Ad36)

Thus far, we have focused on anti-obesity drugs in the pipeline that either directly or indirectly enhance anorexigenic signaling. Vaccination to prevent or treat obesity might potentially be a novel therapeutic approach. Vaccination has traditionally been utilized to eradicate or prevent infectious disease and in some cases, prophylax against cervical or hepatocellular carcinoma by soliciting an immune response to foreign weakened or killed antigens and generating neutralizing antibodies which eliminate the antigen from the body [93]. Key concept in the development of anti-obesity vaccines would be to possibly suppress appetite-stimulating hormones and/or block nutrient absorption.

Ghrelin, the only orexigenic hormone, secreted by the fundus cells of the stomach, has been a target for potential vaccination. Anti-ghrelin vaccine has been shown to decrease food intake, decrease hypothalamic orexigenic signals, and increase energy expenditure in rodents and pigs [93]. However, human studies have been disappointing with no weight loss shown in clinical trials despite a strong response in ghrelin autoantibodies after four injections of anti-ghrelin vaccine vs placebo at weeks 0, 4, 8, and 16 [93, 94] though a different study showed that IgG anti-ghrelin autoantibodies are able to protect ghrelin from degradation, suggesting that an autoimmune response may be involved in ghrelin's orexigenic effects [95].

Somatostatin, a peptide hormone produced in the hypothalamus and other tissues such as the gastrointestinal system inhibits growth hormone (GH) and insulin-like growth factor 1 (IGF-1) secretion. Reduced GH basal secretion has been associated with obesity and increased adiposity, and thus, the principle behind somatostatin vaccination is to remove inhibitory effects of somatostatin and to increase endogenous levels of GH and IGF-1 [96]. In animal mouse studies, however, vaccination did not affect changes in food intake, though a 10% decrease in body weight gain was noted under a high-fat diet [97].

Adenovirus 36 (Ad36) influences the risk of obesity in humans, characterized by increased inflammation and adiposity [98, 99]. In a proof-of-concept study, mice were injected with live Ad36 vaccine and compared to the control group (unvaccinated) after 14 weeks. The control group showed 17% greater body weight and 20% more epididymal fats compared to vaccinated group, which also had decreased inflammatory cytokines and macrophages in fat tissue [100]. Prophylactic vaccination against virus-induced obesity might also be an anti-obesity therapeutic possibility in the near future.

Conclusion

Given the enormous costs and high disease burden of obesity, current pharmacological therapies are not sufficient to address the clinical heterogeneity including side effects and contraindications that can factor into a treatment algorithm for a patient with obesity. Despite a checkered history of past obesity drug development, current approved anti-obesity medications along with newer promising therapies are on the horizon. These therapies provide hope for increasing the medicinal armoire against obesity with more effective treatment strategies, whether in monotherapy or combination. As our understanding of the disease process improves and sustained success is achieved with these drugs, it might be possible to finally easily approach a very complex disease from a clinical therapeutic standpoint.

Contributions

GS and CMA researched data for the article, made substantial contributions to discussions of the content, wrote the article, and reviewed and/or edited the article before submission. No funding was provided for the drafting of this manuscript.

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Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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