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New advances in models and strategies for developing anti-obesity drugs

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Abstract

Introduction—Obesity is a worldwide pandemic. Obesity-related health and economic costs are staggering. Existing strategies to combat obesity through lifestyle improvements and medical intervention have had limited success. Pharmacotherapy, in combination with lifestyle modification, may play a vital role in reversing the disease burden. However, past and current weight-loss medications have had serious safety risks, notably cardiovascular and psychiatric events.

Areas covered—We review the strategies for designing new anti-obesity drugs by describing those currently in development. We describe their target, mechanism of action, and developmental or regulatory status. We also discuss the problem of weight regain following weight loss, and its relevance to the long-term success of anti-obesity pharmacotherapy.

Expert opinion—For weight management drugs to achieve the safety and efficacy required to be impactful, current studies are uncovering and characterizing new targets, including new signaling circuits and hormones regulating appetite and metabolism, and re-evaluating the role of pharmacotherapy in weight management. To avoid the safety failures of many past weight-loss drugs, the models and strategies covered in this article incorporate recent advances in knowledge and technology. We discuss the emergence of cGMP signaling as a potentially transformative target in weight management. Modulating cGMP signaling may represent an ideal goal for an anti-obesity pharmacotherapy, reflecting some of the major themes described in the present review: targeting pathways that are newly realized as relevant for weight management; promoting safety by re-purposing drugs that are safe, proven, and approved for clinical use; and having a synergistic effect on multiple, reinforcing pathways.

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Keywords

anti-obesity drugs; appetite; cGMP; metabolism; obesity; weight regain

1. Introduction

Obesity is a global pandemic. Its prevalence has more than doubled in the last 30 years, resulting in a staggering disease burden in both the US and around the world [1]. As of 2008, the prevalence of overweight and obesity in US adults stood at 68.2% and 33.8%, respectively, and the global burden was estimated at 1.5 billion overweight and 500 million obese [2]. In fact, the global overweight population has eclipsed that of underfed [1]. Furthermore, the prevalence of overweight and obesity in children has more than tripled over the last 30 years [3,4]. In 2010, nearly 12.5 million children in the US and over 40 million worldwide were obese [2]. Childhood obesity has extended traditionally adult-onset diseases like type 2 diabetes and heart disease to children [3,4]. Moreover, obesity in childhood predicts obesity as adults, putting this population at an early disadvantage in terms of health outcomes [3,4]. Obesity is complicated by its myriad associated comorbidities, which include cancer, diabetes, and heart disease [5–7]. With over 2.8 million deaths per year attributable to overweight and obesity, they constitute the fifth leading risk for global deaths [2]. The prevalence of obesity and related diseases is threatening the health systems of wealthy and poor countries alike. In 2008, US medical costs attributable to obesity were estimated at US \$147 billion [8].

The pharmaceutical industry has recognized and responded to the development of a large and willing market for weight management medication. However, the rapidity of obesity's rise as a global health concern has largely outstripped the development of drugs meeting the regulatory criteria for both safety and efficacy. As of January 2013, only three drugs were approved by the FDA (US Food and Drug Administration) for long-term weight management: orlistat (AlliTM, GlaxoSmithKline; Xenical®, Roche); lorcaserin (Belviq®, Arena Pharmaceuticals); and phentermine/topiramate extended-release (QsymiaTM, Vivus). Notably, lorcaserin and phentermine/topiramate have yet to receive approval by the European Medicines Agency (EMA). Furthermore, despite their FDA approval, all three drugs are associated with troubling safety concerns, including carcinogenic, cardiovascular, hepatotoxic, and psychiatric adverse effects [9].

These issues highlight both the urgency for solutions to the unmet clinical need as well as the primacy of the regulatory agencies' duty to ensure efficacy and safety. To win FDA approval, a prospective drug must induce a statistically significant weight loss of at least 5% at one year when compared to placebo, and at least 35% of patients must achieve at least a 5% weight loss and show improvement in metabolic biomarkers [10]. The drug must also be safe for use in the intended population. The obese population is heterogeneous, ranging from relatively healthy to very sick individuals. The inherent complexity of this population appropriately raises safety concerns over new drugs, especially because an obesity drug could represent lifelong therapy. Therefore, efforts are underway to better understand the regulation of appetite, lipogenesis, and metabolism and to uncover new molecular targets. These discoveries may lead to new medications to treat or prevent obesity, improving both

the efficacy and safety required for advancing the role of pharmacotherapy in weight management.

2. History of anti-obesity drugs

Surveying the history of weight-loss drugs reveals that pharmaceutical approaches have long been employed for weight management. Unfortunately, this history is equally rife with safety problems. In the 1890s, sheep thyroid extract was used to increase metabolic rate and induce weight loss in euthyroid patients, but this treatment was ultimately responsible for an increase in cardiac arrhythmias and cardiac arrest [11]. In the 1930s, the drug 2,4-dinitrophenol was a very effective and popular weight-loss drug until the discovery that it caused agranulocytosis, cataracts, dermatitis, and fatal hyperthermia [12].

In 1947, amphetamine was approved for obesity treatment in the US, but it was soon shown to have addictive properties. Nonetheless, in the 1950s, other related sympathomimetic drugs, such as phentermine and diethylpropion, achieved widespread use. During the 1940s–1960s, amphetamines were used in “rainbow” pill regimens that also included digitalis, diuretics, laxatives, and thyroid hormone, along with barbiturates to counteract the nervousness and hyperactivity induced by the stimulants. This cocktail proved disastrous, causing myocardial toxicity and sudden death in many patients, which led to the decline of these pill regimens [13]. In the late 1960s, the use of Aminorex, an amphetamine analog marketed in Europe, caused chronic pulmonary hypertension in patients, with ~50% mortality [14].

During the 1980s–1990s, the amphetamine analog fenfluramine was widely prescribed as an appetite suppressant. In 1992, fenfluramine was combined with phentermine and marketed as the popular drug Fen-Phen. Its popularity helped to reveal that Fen-Phen caused pulmonary hypertension and valvular heart disease, leading to the withdrawal of fenfluramine and its derivative, dexfenfluramine, from the market in 1997, as well as thousands of product liability lawsuits and billions of dollars in legal damages [15].

Since the 1970s, the amphetamine analog phenylpropanolamine (PPA) was available in cough and cold remedies and appetite suppressants and used for unlicensed anti-obesity treatment. In 2000, PPA was demonstrated to cause intracranial bleeding and strokes [16], prompting the FDA to eventually remove it from over-the-counter products in 2005 [17]. Notably, PPA is still available in prescription decongestants in Europe and its use is completely derestricted in the United Kingdom. In 2004, the FDA banned ephedra alkaloids, another common ingredient in dietary supplements, because of its adverse effects, including heart attacks, hypertension, palpitations, strokes, and sudden death [18].

In 2008, the FDA and EMA rejected Rimonabant, an endocannabinoid (CB₁ receptor) inverse agonist, because of psychiatric risks, including depression and suicide. Consequently, Sanofi-Aventis terminated studies on Rimonabant and discontinued development of other CB₁ antagonists. 1997 saw the introduction of the amphetamine analog sibutramine, which inhibited the reuptake of serotonin, norepinephrine, and dopamine. However, in 2010, Abbott Laboratories withdrew sibutramine after increasing concerns over cardiovascular events prompted regulatory actions by the FDA and EMA.

Currently, the lipase inhibitor orlistat (Alli™, GlaxoSmithKline; Xenical®, Roche) is the only drug that is approved by both the FDA and the EMA for chronic weight management. Orlistat is also the only FDA-approved weight-loss drug that is available without a prescription. It was approved in 1999 for prescription sale and 2007 for over-the-counter sale. Orlistat is a gastrointestinal inhibitor of pancreatic lipases that reduces the absorption of fat. Its most common adverse effect is steatorrhea. In 2010, the FDA issued a warning after reports of severe hepatotoxicity. In 2011, a Canadian review reported an increase in acute nephrotoxicity within one year of starting orlistat [19]. Also in 2011, the consumer advocacy group and drug safety watchdog Public Citizen requested that the FDA ban orlistat because of hepatotoxicity, acute pancreatitis, and kidney stones [20]. Simultaneously, GlaxoSmithKline announced its plan to divest 19 of its non-prescription products, including Alli, by the end of 2011 in an effort to streamline their over-the-counter profile, although manufacturing issues have delayed the sale of Alli, as of January 2013 [21].

In 2010, the FDA rejected two proposed weight-loss drugs, lorcaserin (Belviq®, Arena Pharmaceuticals) and phentermine/topiramate extended-release (Qsymia™, Vivus) over safety and efficacy issues. Major concerns over lorcaserin included limited efficacy, carcinogenesis, cardiovascular events, cognitive impairment, and psychiatric disorders. Major concerns over phentermine/topiramate included cardiovascular events, fetal toxicity, and suicidal ideation. In 2012, the FDA reversed its position and granted approval to both lorcaserin and phentermine/topiramate. Notably, though, the FDA has required postmarketing safety studies to address the lingering cardiovascular concerns. Furthermore, the EMA has yet to grant approval to either drug. Table 1 lists the anti-obesity medications currently in use, including mechanisms of action and approval status.

The troubled history of weight-loss drugs illustrates the need for new, safer, and more effective approaches to treat and prevent obesity and its associated sequelae. In the next section, we discuss the drugs that are currently under development based on their target and mechanism of action. Table 2 lists the anti-obesity medications currently in development, including targets, mechanisms of action, and approval status.

3. Obesity drugs under development

3.1 Central neurotransmitters

3.1.1 Hypothalamic neurotransmitters—The arcuate nucleus (ARC) of the hypothalamus is the primary site in the central nervous system (CNS) where appetite is regulated by peripheral signaling hormones. Two main types of neurons regulate appetite in this region: 1) anorexigenic (appetite-suppressing) signals are mediated by neurons expressing the neuropeptides pro-opiomelanocortin (POMC) and cocaine- and amphetamine-regulated transcript (CART); and 2) orexigenic (appetite-stimulating) signals are mediated by neurons expressing the neuropeptides agouti-related peptide (AgRP) and neuropeptide Y (NPY). These neurons send projections elsewhere, including the dorsomedial nucleus, paraventricular nucleus, lateral hypothalamus, and prefrontal area. These areas in turn relay the signals to secondary neurons that then process and integrate the information [22]

Melanin-concentrating hormone (MCH) is a potent orexigenic neuropeptide. It is expressed in second-order neurons of the lateral and prefrontal hypothalamus. Two pharmacologic antagonists of the MCH-1 receptor (MCH-1R), BMS-830216 (Bristol-Myers Squibb) and ALB-127158(a) (AMRI) are in phase I/II clinical testing [23,24]. Cleavage of POMC yields several hormones, including α -melanocyte stimulating hormone (α -MSH). Melanocortins induce anorexigenesis through activation of the melanocortin 3 (MC3R) and melanocortin 4 (MC4R) receptors. Mutations in MC4R represent a genetic basis of obesity. An agonist of MC4R, MK-0493 (Merck), showed promising results in rodent models of diet-induced obesity. However, it failed to demonstrate statistically significant results in phase II clinical trials [25]. Another agonist, a small peptide with higher specificity for MC4R (RM-493; Rhythm) has shown promising results in preclinical testing [26]. As the evidence for anti-obesity effects of MC4R agonism grows, drug development studies continue to search for molecular chaperones and selective small agonists for MC4R [27]. MC4R is, however, another anti-obesity target that may raise significant safety concerns due to the role of melanocortins in cardiovascular and sexual function [28].

NPY is another potent orexigenic neuropeptide, and activation of G protein-coupled receptors (GPCRs) Y1 and Y5 mediates NPY-induced feeding [29]. Inhibition of this signaling reduces food intake and body weight in mice [30,31]. In 2010, Merck abandoned the development of the NPY receptor antagonist MK-0557 after results from a year-long study produced weight loss that was statistically significant but not clinically meaningful (less than 3 kg) [32]. However, S-2367 (Velneperit; Shionogi), another Y5 receptor inhibitor, induced significant weight loss over the course of one year in two double-blind studies [33]. Obese patients taking 800 mg daily in combination with a reduced-calorie diet had 5% or greater weight loss compared to placebo. In addition, S-2367 also improved other endpoints, including reduction in waist circumference and improved lipid panels. S-2367 was well-tolerated over the course of these studies and continues to be studied in phase II clinical trials. An inhibitor of AgRP (TTP-435, TransTech Pharma) is also in phase II trials [34].

3.1.2 Monoamine neurotransmitters—Pharmacotherapy targeting monoamine neurotransmitters, such as dopamine, norepinephrine, and serotonin, has shown efficacy in inducing weight loss in patients [35]. However, due to the wide range of neuronal functions mediated by these neurotransmitters, use of such drugs poses risks for addiction, cardiovascular events, hypertension, and tolerance [36].

Dopamine regulates the motivation for food intake. Consistent with this role, recent studies found that dopamine levels spike in response to food stimuli in binge eaters [37]. Dopamine receptor inhibition may consequently represent a weight loss therapeutic strategy. GlaxoSmithKline completed a phase I clinical trial of a D3 antagonist (GSK598809) using fMRI to investigate its effect on food reward and reinforcement in overweight and obese subjects. Results have yet to be released.

Central histamine signaling plays a role in appetite regulation, and modulation of histamine receptor signaling has been shown to alter body weight and food intake in obese mice [38,39]. The inhibition of H₁-histamine receptors has been implicated in the weight gain

associated with antipsychotic drugs. Activation of the H₃-histamine receptor inhibits histamine synthesis and release. Therefore, antagonists targeting the H₃-histamine receptor to raise histamine levels have been a focus for weight-loss drug development. H₃-histamine receptors are predominantly expressed in the CNS, and this limited expression might minimize the off-target effects of a potential drug. The selective H₃-histamine receptor antagonist A-331440 (Abbott Laboratories), induced significant weight loss in mice raised on a high-fat diet, with the highest dose reducing weight to levels comparable to those of mice raised on a low-calorie diet [40]. Another selective H₃-receptor antagonist, HPP404 (TransTechPharma), is in phase I clinical trials [41]. Schering-Plough completed a phase II clinical trial of its H₃-receptor antagonist SCH-497079 [42].

A triple monoamine reuptake inhibitor, tesofensine (NeuroSearch), has produced promising results in phase II clinical trials. Tesofensine was originally developed for treatment of both Alzheimer's and Parkinson's disease. It demonstrated limited effectiveness for those applications but revealed potential for weight loss therapy. In a phase II clinical trial, obese patients received 0.25, 0.5, or 1 mg of tesofensine or placebo over 24 weeks after a 2 week run-in period [43]. Results of this trial showed significant weight loss at all doses when compared to placebo. The most common adverse events were dry mouth, nausea, constipation, hard stools, diarrhea, and insomnia. Increases in heart rate and blood pressure were also observed, which may limit further increases in dosing. In another phase II trial with overweight and moderately obese individuals, 2.0 mg of tesofensine was given daily for 7 days and 1.0 mg given daily for another 7 days [44]. The treatment group showed a 1.8 kg weight loss above placebo, higher satiety ratings and lower food intake. In May 2011, NeuroSearch reported its intent to start phase III clinical trials with tesofensine, seeking a partner to help finance the continuing development and commercialization costs [45].

Combination therapy targeting monoamine neurotransmitters is also under development. Contrave (Orexigen) is a combination of bupropion, a dopamine and norepinephrine reuptake inhibitor, and naltrexone, an opioid receptor antagonist. By blocking the autoinhibition of hypothalamic POMC neurons by endogenous β -endorphins, naltrexone potentiates bupropion's stimulation of the POMC neurons and downstream α -MSH neurons [46]. In phase III clinical trials, Contrave demonstrated that patients achieved greater weight loss on a diet and exercise program over 56 weeks with bupropion/naltrexone (6.1 kg) than with placebo (1.4 kg) [47]. In 2011, the FDA rejected Contrave, and requested a large cardiovascular risk trial to address long-term adverse effects before it could approve the drug [47]. Orexigen has begun the requested long-term clinical trial, and its New Drug Application has been submitted and reviewed by the FDA, with potential approval in late 2013 or early 2014. Orexigen has suspended clinical trials for Empatic, a combination of the antiepileptic drug zonisamide and bupropion. In phase II clinical trials with obese patients, Empatic induced greater weight loss when compared to its individual components or placebo [48]. At 24 weeks, patients had shown no evidence of plateau, which suggested that greater weight loss could be achieved in a year-long trial.

3.2 Adipose hormones

3.2.1 Leptin—Leptin is a hormone derived from adipose tissue, and originally called the “obese gene” (*ob*) after mice harboring mutations developed morbid obesity [49]. Humans with congenital leptin deficiency show early-onset obesity that is treatable via leptin replacement therapy [50,51]. Activated leptin receptors in the hypothalamus increase POMC expression and stimulate POMC/CART signaling [52], suppressing AgRP expression and inhibiting NPY/AgRP signaling in the ARC [53–55]. However, obesity is characterized by leptin receptor resistance, and such patients exhibit high circulating levels of the hormone [56]. Consistent with these findings, circulating levels of leptin are correlated with degree of adiposity [56] and feeding state [57]. Thus, leptin as a therapeutic target has proved disappointing due to receptor resistance [58].

Despite this resistance, treatment with the pancreatic hormone amylin notably restores leptin receptor signaling in the hypothalamus in obesity [59]. Amylin and leptin seem to act synergistically in reducing appetite and weight in rats, but synergy with leptin has not been detected with other peptides. Importantly, this resensitization through amylin translates to humans. Overweight and obese patients treated with injections of pramlintide (a synthetic amylin analog) and metreleptin (a synthetic leptin analog) twice daily lost more weight than those on monotherapy [60]. Combination therapy also resulted in sustained weight loss compared to a plateau reached by the placebo group, with low toxicity. In a follow-up, phase II, dose-ranging study, overweight and obese individuals were treated with combination therapy twice daily (b.i.d). A striking effect was observed at the highest doses tested (pramlantide 360 mcg, metreleptin 5mg). Combination therapy patients lost ~11% of body weight compared to patients receiving either agent alone or placebo at ~5.0% and 1.8% respectively [61]. Patients in a 52-week extension of this trial demonstrated sustained weight loss while those receiving placebo regained all their lost weight [60]. Based on these results, pramlintide/metreleptin co-therapy advanced into phase III clinical trials. In March 2011, however, trials for the combination therapy were suspended due to safety concerns over an antibody-related laboratory finding with metreleptin treatment [62].

3.3 Gastrointestinal hormones

3.3.1 Cholecystokinin (CCK)—Cholecystokinin (CCK) is an intestinal peptide which is secreted in response to foods high in fat and protein by the I cells in the duodenum and jejunum [63]. Physiologically, it facilitates digestion and also serves as a neurotransmitter in the CNS [64]. CCK signaling is mediated by the CCK receptor, a seven-transmembrane GPCR. There are two isoforms of the receptor, CCK-A (CCK1) and CCK-B (CCK2). It appears that CCK-A, which is expressed in the pyloric sphincter and in vagal afferents, mediates the CCK effect on satiety. In rodents, CCK-A agonists suppress appetite while receptor deficiency or blockade results in hyperphagia and obesity [65–67]. In humans, the CCK-A receptor antagonist, loxiglumide, induces higher caloric intake [68]. However, CCK effects on weight reduction are limited, which may be due to the development of tolerance after chronic administration in animals [69,70]. Intermittent CCK administration has a mixed effect on food intake, reducing the size but increasing the frequency of meals [71]. GlaxoSmithKline terminated development of the selective CCK-A agonist GI 181771X after it failed to induce weight loss in phase II trials [72]. In addition, chronic CCK administration

in preclinical models induced pancreatitis in animals, raising safety concerns for the development of drugs in this class [73,74]. Notably, however, CCK potentiates appetite and weight reduction by leptin [75], which suggests that combination therapy may hold promise.

3.3.2 Ghrelin—Ghrelin is notably the only known circulating orexigenic hormone. It is cleaved from its precursor prepro-ghrelin and is produced mainly by the gastric fundus. Ghrelin may modulate obesity not only through increased appetite and food intake but also via reduced energy expenditure. In addition to its orexigenic effects, ghrelin has been reported to stimulate the release of growth hormone (GH) through activation of the growth hormone secretagogue receptor (GHS-R) [76], but its physiological relevance on GH release is unclear [77]. Ghrelin regulates hunger and feeding principally through activation of NPY/AgRP neurons in the ARC, although vagal stimulation and other CNS sites expressing GHS-R appear to be involved, including the dorsal raphe nucleus, hippocampus, and mesolimbic reward pathway [78–80]. Long-term energy homeostasis is regulated by ghrelin, and circulating levels of ghrelin are reduced in obese patients but exaggerated in anorexic patients. Decreased ghrelin levels are correlated with weight gain but levels increase substantially with diet-induced weight loss. This in turn may contribute to the difficulty in maintaining the weight loss [81–84]. Interestingly, the success of bariatric surgery has been correlated to inhibition of this diet-induced rise in ghrelin levels [85].

Inhibiting the activity of ghrelin has long been a focus of anti-obesity drug development programs. Direct neutralization of ghrelin was investigated with a first-generation ghrelin vaccine, CYT009-GhrQb (Cytos). Although patients exhibited a strong immune response to ghrelin as evidenced by a robust antibody response, they did not lose weight, which resulted in the discontinuation of this vaccine [86]. Several second-generation vaccines have been developed and shown to decrease feeding, adiposity, and body weight in rodents [87,88]. An alternative strategy utilizing ghrelin-neutralizing RNA Spiegelmer, NOX-B11 (NOXXON Pharma AG), which binds to and inactivates ghrelin, was able to block the orexigenic activity of exogenous ghrelin administration [89]. However the treatment failed to alter food intake in rats [90]. Pharmacologic ghrelin antagonists from Elixir Pharmaceuticals/Novartis and Aeterna Zentaris (AEZS-123) are in various stages of preclinical testing [82,91]. In addition, inhibition of ghrelin *O*-acyltransferase (GOAT), a membrane-bound enzyme that adds to ghrelin an octanoate that is required for receptor binding, may be a worthwhile strategy to reduce ghrelin signaling [92].

3.3.3 Glucagon-like peptide 1 (GLP-1)—Glucagon-like peptide 1 (GLP-1) is a product of the proglucagon gene which is generated by enteroendocrine L cells in the ileum and proximal colon [93]. Post-prandial secretion of GLP-1 results in increased insulin secretion, suppression of glucagon, reduced gastric emptying, and decreased food intake. The GLP-1 receptor (GLP-1R) is a GPCR expressed in the heart, kidney, lung, pancreas, CNS, and PNS, including the nucleus tractus solitarius (NTS) of the dorsal vagal complex (DVC), and the ARC [93]. Administration of GLP-1 in animals and humans induces satiety and weight loss [94–97]. However, its utility is limited by rapid proteolysis by dipeptidyl peptidase IV (DPP-IV) [98].

Proteolysis-resistant GLP-1 analogs have been developed to combat this issue and include liraglutide (Victoza; Novo Nordisk) and exenatide (Byetta; Amylin/Eli Lilly). Clinically these drugs are currently FDA-approved for adjuvant therapy in type 2 diabetes. Several meta-analyses of type 2 diabetic patients on GLP-1 analogs have shown significant reductions in body weight when compared to patients either on placebo or receiving insulin therapy [99–102]. Weight loss induced by GLP-1 analogs was dose-dependent, progressive, and did not plateau by 30 weeks. In all cases, patients on exenatide lost more weight than those on liraglutide [99]. In a clinical trial of non-diabetic obese individuals, liraglutide induced a mean of ~6.0 kg in weight loss, and >35% of the subjects treated with the highest dose achieved a reduction of 10% baseline weight. Currently, liraglutide is in phase III clinical trials to win FDA approval for obesity.

A long-acting release formulation of exenatide (exenatide-LAR; Amylin), which is injected once weekly, has been developed to improve dosing regimen, as the original drugs required daily injections. In a 15-week trial in diabetic patients, exenatide-LAR was shown to improve body weight. Two years of weekly exenatide-LAR treatment resulted in a weight loss of 5.8 lbs. In 2010, however, the FDA issued a complete response letter expressing concerns about possible cardiac toxicity with exenatide-LAR and requested additional safety studies to be completed before approving use in diabetic patients. Additionally, a long-acting oral GLP-1 analog (NN9924; Novo Nordisk/Emisphere) utilizing SNAC (sodium N-[8-(2-hydroxybenzoyl) amino] caprylate technology is in phase I clinical trials in the UK [103]. One study examining oral GLP-1 analog (2.0 mg) produced a significant reduction ($13.6 \pm 3.6\%$) of total food intake in 12 healthy male subjects, but only a weak effect was seen on hunger and satiety [104]. Additionally, DPP-IV inhibitors have been developed, which include vildagliptin (Novartis), saxagliptin (Onglyza; Astra Zeneca) and sitagliptin (Januvia; Merck). These drugs increase GLP-1 levels by inhibiting proteolysis, have been developed. However, these drugs have been shown to have little or no effect on weight loss [99–102].

3.3.4 Oxyntomodulin (OXM)—Like GLP-1, oxyntomodulin (OXM) is a potent anorexigenic peptide which also produced from the processing of preproglucagon. OXM is secreted postprandially along with GLP-1 by the L cells of the colon but has minimal function in insulin homeostasis as an incretin. It is thought that OXM exerts its anorectic effects via activation of central GLP-1Rs as well as stimulation of POMC neurons in the ARC. In human studies, IV infusion of OXM suppressed appetite and reduced feeding, while also increasing energy expenditure [105,106]. However, the need for continuous infusions of OXM limits its use as an anti-obesity therapeutic. Two long-acting OXM analogs are currently under development: TKS-1225 (Thiakis/Wyeth/Pfizer) and OXY-RPEG (PROLOR). TKS-1225 entered phase I clinical trials in 2008. PROLOR Biotech has used their reversible pegylation technology, which increases the half-life of therapeutic peptides and small molecules, to develop [107]. This technology seems to increase not only the half-life of OXM but also its potency. In a preclinical study, OXY-RPEG demonstrated significantly greater weight loss, reduction of food intake, and duration of weight loss activity when compared to OXM injected twice daily [107].

3.3.5 Peptide YY (PYY)—Peptide YY (PYY) is a potent anorexigenic peptide of the pancreatic polypeptide family, which binds to the GPCRs Y1–Y5 [29]. It is produced in the gut by the L cells of the terminal ileum and colon and is secreted into the circulation in response to a meal [108]. PYY stimulates absorption of fluids and electrolytes by the gastrointestinal tract [109], reduces gastric and pancreatic secretions, and delays gastric emptying [108]. The circulating form, PYY_{3–36}, has high affinity for the Y2 receptors. It is believed that this peptide suppresses appetite by activating pre-synaptic Y2R in the ARC, which in turn inhibits orexigenic NPY/AgRP neurons. Interestingly, humans and rodents have decreased circulating levels of postprandial PYY in obesity compared to lean controls [110]. Following bariatric surgery, plasma levels of PYY rise back to normal, which may contribute to the efficacy of bariatric surgery in producing long-term weight loss. Since obesity causes a hormone deficiency, rather than resistance, to PYY, it has immense potential as a therapeutic target. In studies conducted in healthy subjects, continuous infusion of PYY reduced hunger and caloric intake by 36% in a dose dependent fashion [111,112], with a similar decrease seen in obese patients [105].

Since degradation is a major hurdle in the use of therapeutic peptides, technologies are in development to create stable forms of PYY and others that enhance delivery. A selective Y2R analog of PYY corresponding to residues 13–36 conjugated to polyethylene glycol (PEG) (Merck) was effective in reducing food intake and body weight in rodents [113]. However, intranasal delivery of PYY (Nastech/Merck) failed to induce weight loss in humans [114]. Utilizing SNAC carrier technology (Emisphere Technologies), a PYY_{3–36} oral formulation was developed, which was rapidly absorbed by the GI tract. Despite effective delivery, the drug caused only a non-significant reduction of energy intake ($12.0 \pm 6.7\%$, vs placebo) and only weak effects on hunger and satiety in healthy human subjects [104]. Interestingly, a synergistic effect in both energy intake and fullness was seen when GLP-1 was co-administered, suggesting the potential for combination therapy [104]. PYY_{3–36} or GLP-1 treatment, either alone or in combination, caused a decrease in the plasma level of the orexigenic peptide ghrelin during meal consumption [104]. Despite these promising characteristics, there is a notable therapeutic limitation of PYY; treated patients may exhibit nausea and vomiting in a dose-dependent manner [104,112,114].

3.4 Pancreatic hormones

3.4.1 Amylin—Amylin, also known as islet amyloid polypeptide (IAPP), is secreted along with insulin by pancreatic β -cells [115], and type 1 diabetics are deficient in both hormones. Fasting plasma levels of amylin are low, and increase after meal consumption [116]. Physiologically, amylin acts not only to regulate glucose levels in synergy with insulin, but also drives anorectic functions. Receptors for the hormone are expressed in certain CNS regions, including the area postrema of the dorsal vagal complex [115], and vagal signaling is critical to amylin-mediated appetite suppression [117,118]. Administration of amylin by constant infusion over 10 days reduced feeding and adiposity in laboratory animals [119]. Pramlintide, a synthetic amylin analog, is approved for the treatment of diabetes (Symlin; Amylin) [120]. This drug is similar to amylin both pharmacokinetically and pharmacodynamically [121]. Interestingly, diabetics treated with pramlintide exhibited marked reduction in body weight in both type 1 and 2 diabetics [122–125]. A pooled, *post-*

hoc analysis in type 2 diabetic subjects demonstrated that pramlintide, at 120 µg b.i.d. or 150 µg q.d., induced an average weight loss of 2.6 kg over 52 weeks of therapy [125]. Adverse effects were minimal, consisting of a transient increase in mild-to-moderate nausea and headache [122–125]. Davalintide, Amylin Pharmaceuticals's second-generation amylin analog that has enhanced amylin pharmacologic properties, is in phase II clinical trials.

3.4.2 Pancreatic polypeptide (PP)—Pancreatic polypeptide (PP) is a satiety peptide that possibly originated through duplication of the *PYY* gene [126]. PP is primarily produced in the pancreas where it binds with highest affinity to Y4 and Y5 receptors [29]. Levels of PP rise in the circulation after meal ingestion proportionally to caloric intake and remain elevated for up to six hours [127]. Other peripheral hormones, including ghrelin, also induce PP secretion [128]. PP's effects on appetite are mainly mediated in the area postrema of the dorsal vagal complex, which induces changes in levels of hypothalamic peptides [129]. Furthermore, peripheral administration of PP has been reported to decrease appetite and weight gain in rodents [129,130]. Plasma levels of PP are lower in obese patients [131], while PP responses are exaggerated in patients with anorexia nervosa [132]. IV infusion of PP (10 pmol/kg/min) in healthy subjects resulted in a reduced appetite and caloric intake by 22%, and proved effective over 24 hours [133]. As with other peptides, PP has a short half-life [134], extended duration formulations of Y2R or Y4R agonists may be necessary for long-term success in appetite control and weight loss. PP1420 (Wellcome Trust), a synthetic analog of PP with an increased half-life, is currently in phase I clinical trials (NCT01052493). A Y2/Y4-receptor agonist, Obinipitide (7TM Pharma), and a selective Y4-receptor agonist, TM30339 (7TM Pharma), are in phase I/II clinical trials [120,121,135,136].

3.5 Other targets

3.5.1 11 β -hydroxysteroid dehydrogenases (11 β -HSDs)—A class of enzymes known as 11 β -hydroxysteroid dehydrogenases (11 β -HSDs) plays a role in many pathologic processes including obesity, type 2 diabetes and hypertension. Two isoforms have been identified: 11 β -HSD1 and 11 β -HSD2. These enzymes play an important role in glucocorticoid metabolism, catalyzing the transformation between active cortisol and inactive cortisone. Excess glucocorticoids produce visceral obesity and diabetes. 11 β -HSD1 is present in liver and adipose tissue, and enzyme activity is modulated by other factors including glucocorticoids, stress, sex steroids, growth hormone, cytokines and PPAR agonists. Importantly, levels of 11 β -HSD1 are markedly increased in adipose tissue of obese individuals. Transgenic mice with increased 11 β -HSD1 activity exhibit obese symptoms, including excess visceral fat, insulin resistance, and dyslipidemia [137]. These findings have prompted development of 11 β -HSD1 inhibitors for the treatment of diabetes and obesity. Astra Zeneca has an 11 β -HSD1 inhibitor in phase I clinical trials (AZD8329) and Incyte (INCB13739) recently completed a phase I study in obese individuals (NCT00398619).

3.5.2 Diglyceride acyltransferase (DGAT)—Diglyceride acyltransferase (DGAT) catalyzes the final reaction of triglyceride synthesis. DGAT functions in adipose tissue and may therefore play a role in obesity and its treatment. Indeed, mice lacking DGAT expression are lean and resistant to diet-induced obesity [138]. In light of these findings,

AZD7687 (Astra Zeneca) was developed, a DGAT inhibitor currently in phase I clinical trials for treatment of obesity and diabetes. Additionally, Takeda Pharmaceuticals demonstrated that another DGAT inhibitor stimulated lipid metabolism in muscle and induced weight loss in animal models of obesity [139].

3.5.3 Lipase inhibitors—Pancreatic lipase acts to hydrolyze triglycerides in the diet, thereby converting fats into more absorbable free fatty acids. Lipase inhibitor treatment is used clinically and generally results in excretion of unabsorbed triglycerides and, consequently, reduced caloric intake. Orlistat was the first drug in this class to be approved by the FDA in 1999. Undesirable gastrointestinal side effects including steatorrhea have limited the success of the first generation drug on the market. An experimental second-generation lipase inhibitor, cetilistat (Alizyme/Takeda) is thought to have an improved side-effect profile due to differences in molecular structure. In a phase II clinical trial, cetilistat (80 and 120 mg) produced a significant weight loss over placebo that was comparable to that elicited by orlistat [140]. Cetilistat is currently in phase III clinical trials in Japan.

3.5.4 Methionine aminopeptidase 2 (MetAP2)—Beloranib (Zafgen), also known as ZGN-433 and ZGN-440, is an inhibitor of methionine aminopeptidase 2 (MetAP2), which is an enzyme critical to post-translational processing and protein synthesis. This compound was initially developed as an anti-cancer agent targeting MetAP2's role in tumor vascularization and metastasis [141]. Notably in these studies, preclinical data suggested possible efficacy in body weight control, although the precise mechanism of action for beloranib in obesity treatment is not clear. It is believed that MetAP2 inhibitors exert their effects by re-establishing balance in fat metabolism, leading to weight loss and improved glucose tolerance. Oral gavage with fumagillin, another MetAP2 inhibitor, reduced adipose tissue formation in diet-induced obese mice [142]. In a phase Ib study with severely obese patients (body mass index = 32–35 kg/m²), beloranib (0.9 mg/m²) resulted in a median weight loss of 1 kg per week and 3.1% over 26 days relative to placebo controls [143]. Beloranib was administered by intravenous infusion and a reduction in hunger and meaningful changes in lipid parameters were observed. The drug was well-tolerated over the course of the experiment. In August 2012, Zafgen initiated beloranib phase II studies, which are scheduled for completion in June 2013.

4. Weight regain

A major barrier to obesity therapy is weight regain. This regain is a common occurrence in patients who have lost weight, regardless of the method used to induce weight loss (bariatric surgery, lifestyle modification, or pharmacotherapy) [144]. Approximately 30–35% of lost weight is regained one year following lifestyle-induced weight loss and 50% of patients will return to their baseline weight by the fifth year out from weight loss [145]. Further, according to the National Health and Nutrition Examination Survey NHANES (1999–2006), only 1 in 6 overweight and obese adults reported maintaining weight loss of at least 10% for 1 year, at any point in their lives [146]. In fact, one reason for the increased efficacy of bariatric surgery relative to other interventions is an increased durability of the weight loss response [147]. Thus, mechanisms of weight regain are garnering more attention as therapeutic targets to improve outcomes in obese patients.

Changes in energy expenditure have been implicated in weight regain. There are two types of energy expenditure: resting energy expenditure (REE) is defined as the energy needed to fuel minimal daily functions of cells and organs; total energy expenditure (TEE) represents a compilation of expenditures, including resting metabolic rate, diet-induced thermogenesis and activity-related energy expenditure [148–150]. Interestingly, weight loss leads to a compensatory decrease in REE [151], which accounts for approximately 60 percent of TEE in humans [152]. This change is known as “adaptive thermogenesis,” and evidence suggests that these changes increase hunger, promoting weight regain [152]. Therefore, changes in energy expenditure may represent a metabolic and physiologic response resisting the maintenance of the decreased body weight.

In addition to changes in energy expenditure, weight loss also results in compensatory changes to the hormonal and neuronal milieu that governs body weight and feeding. A recent human study investigated these compensatory mechanisms following weight loss in obese patients [153]. Following weight loss, patients exhibited significant and persistent (beyond one year) reductions in levels of leptin, peptide YY, cholecystokinin and insulin, and increases in levels of ghrelin and pancreatic polypeptide, as well as an increase in subjective appetite. Canonically, the observed hormonal changes are all permissive of weight regain (with the exception of increased pancreatic polypeptide). Further, the decrease in leptin exhibited a strong linear correlation with weight regain in patients. These findings are consistent with other recent reports of decreased release of the satiety hormones PYY and GLP-1 secondary to weight loss [154,155].

Importantly, these alterations promoting weight regain generally involve pathways already being studied for anti-obesity pharmacotherapy. Thus, as our understanding of the interplay of factors promoting weight regain improves, drugs that translate this understanding into therapeutic strategies may be forthcoming. Therefore, further investigation is warranted to define these mechanisms and improve our understanding of these compensatory mechanisms.

5. Conclusion

Regulatory trepidation regarding the development of weight loss pharmacotherapy is justified in light of the series of safety-related failures of the past. Therefore, the key to successful drug development and deployment seems to lie in an appropriate risk-benefit balance, coupled to a better understanding of the mechanisms underlying appetite and metabolism. Regulatory agencies and the pharmaceutical industry must work together towards a clinical paradigm whereby the next generation of targeted therapies will be developed to maximize safety and efficacy by pursuing the next generation of drug targets and strategies.

Obstacles impeding the development of new medications are the sheer complexity of the pathways involved and the limits in translating preclinical data to human studies. Nonetheless, it is certainly worthwhile to pursue the development of safe and effective drugs to address the unmet clinical need. The scope of the obesity problem demands urgent action to improve the available therapeutic options for obese patients. Lifestyle modification alone

has been largely disappointing. Bariatric surgery, despite its efficacy, has yet to shed enough risk or cost to make it the first or best option for most patients. In light of the intricate interplay of factors regulating energy homeostasis, the most effective therapeutic model may involve simultaneous targeting of multiple pathways. Recent evidence supports this hypothesis. Perhaps the most robust evidence supports the combination therapy using PYY and GLP-1. Co-administration of these peptides has been shown in multiple studies to have an additive effect on neurologic satiety centers and appetite reduction in both rodents and man [156,157]. Additionally, another GLP-1 receptor agonist, oxyntomodulin, has also been shown to exhibit a positive interaction with PYY in inducing satiety [158]. Similar interactions have been shown for other combinations, most notably GLP-1 and CCK [159]. As our understanding of the web of metabolic pathways becomes clearer, perhaps these combinational therapies will solve the riddle of clinical efficacy to meet the unmet need for obesity interventions.

6. Expert opinion

Cyclic GMP (cGMP) is an important second messenger generated by the family of guanylyl cyclase receptor enzymes, which are expressed in many tissues, including the brain, heart, and intestine [160]. Guanylyl cyclases are activated upon binding by their cognate ligands, which include the natriuretic peptides (ANP, BNP, CNP), the intestinal peptides guanylin and uroguanylin, and nitric oxide (NO). Cyclic GMP is degraded by cGMP-hydrolyzing phosphodiesterases (PDEs). Signaling through cGMP, guanylyl cyclases regulate a variety of physiologic processes, including intestinal electrolyte and water homeostasis, platelet activation, retinal phototransduction, and vascular smooth muscle relaxation [160]. Consequently, modulating cGMP levels has long been an active area of interventional pharmacology: nitrates such as glycerol trinitrate are used to induce vasodilation and treat angina, hypertension, and myocardial infarction; PDE inhibition is used to sustain cGMP levels and treat pulmonary hypertension and erectile dysfunction [161,162]. Recent discoveries have revealed that cGMP-mediated pathways underlie physiologic processes central to energy homeostasis [162,163].

Guanylyl cyclase C (GUCY2C) is a member of the particulate guanylyl cyclase family, whose expression has been historically restricted to the intestinal epithelium [160,164,165]. GUCY2C is activated by the endogenous hormones guanylin and uroguanylin, which are also produced in the intestinal epithelium and activate GUCY2C in a paracrine fashion. Binding by its cognate ligands activates GUCY2C to produce cGMP. GUCY2C signaling maintains a set of homeostatic mechanisms that are vital to intestinal health, including electrolyte and fluid balance, proliferation and differentiation along the intestinal crypt-villus axis, genomic integrity via DNA damage repair, cellular metabolism, and the tight junctional barrier function of the intestinal epithelium [166,167].

Recent studies have revealed a new GUCY2C function in the mouse brain and expanded the homeostatic role of GUCY2C. GUCY2C represents one end of a gut-brain endocrine axis: GUCY2C is expressed in the hypothalamus, and responsive to uroguanylin, which is produced in the intestine and released postprandially into the circulation to activate hypothalamic GUCY2C and signal energy levels (Figure 2) [168]. Furthermore, Gucy2c

knockout mice (*Gucy2c*^{-/-}) mice have dysregulated energy homeostasis, compared to wildtype mice (*Gucy2c*^{+/+}) [168]. *Gucy2c*^{-/-} mice lack nutrient-induced satiety responses, are hyperphagic, and have an increased rate of weight gain. They display obesity-associated disorders, including elevated adiposity, hypertriglyceridemia, hyperleptinemia, hyperinsulinemia, and impaired glycemic control, and develop metabolic disease including fulminant diabetes, left ventricular hypertrophy, and hepatic steatosis [168].

The discovery of a new gut-brain axis regulating appetite, body weight, and metabolism through GUCY2C signaling [168] offers a potential new target for the development of pharmacotherapies to treat obesity. Targeting GUCY2C signaling would leverage an endogenous endocrine mechanism mediating energy homeostasis. Moreover, GUCY2C activation may be achievable with reformulations of existing drugs like the synthetic GUCY2C peptide agonist, linaclotide (LinzessTM, Ironwood Pharmaceuticals, Forest Laboratories), which has already been approved by the FDA and EMA to treat disorders of gastrointestinal motility (chronic idiopathic constipation, irritable bowel syndrome with constipation) [169,170]. In clinical trials, patients with chronic constipation improved after 12 or 26 weeks of treatment with 290 µg oral linaclotide, which had no systemic exposure, was well-tolerated, and had minimal adverse effects, diarrhea being the most common [170].

Mammalian adipose tissue is mainly composed of two types: white adipose tissue (WAT) and brown adipose tissue (BAT) [171]. WAT is responsible for energy storage in the form of triglycerides, and for endocrine functions. BAT is rich in mitochondria and uncoupling protein 1 (UCP1), by which it dissipates energy in the form of heat, a process known as thermogenesis. Therefore, BAT promotes increased energy expenditure. Consequently, the “browning” of WAT to increase the development or differentiation of BAT may be an attractive strategy to induce weight loss. Also, adipocytes have high expression of the natriuretic peptide receptors [172]. Moreover, cGMP is a key regulator of mitochondrial biogenesis and brown fat differentiation [173,174]. Studies conducted *in vitro* and in mice demonstrated that natriuretic peptides activated these guanylyl cyclases and increased cGMP concentrations [172]. This signaling led to an expansion of BAT and increased thermogenesis. Also, increasing cGMP levels through transgenic mouse models or sildenafil-mediated PDE5 inhibition was able to drive BAT differentiation [175,176]. Therefore, increasing the BAT/WAT ratio via cGMP pathways may be a promising strategy to increase BAT-mediated energy expenditure and decrease WAT-mediated fat storage. Moreover, implementing this strategy may be significantly facilitated by the ready availability of approved PDE5 inhibitors, such as sildenafil. Sildenafil is currently used to treat erectile dysfunction and pulmonary arterial hypertension. Its dosage and safety in long-term management of weight and metabolism would have to be determined.

These discoveries not only expand our knowledge of cGMP function but also offer new signaling circuits to leverage for weight management. Furthermore, since both satiety and thermogenesis are increased by activation of these cGMP pathways, driving this pathway through drug administration would conceivably drive both of these physiologic processes in the same direction, resulting in weight loss by mutual reinforcement. Moreover, the existence of an established market for medications targeting cGMP pathways suggests the possibility of utilizing off-the-shelf pharmacological approaches, with FDA- and EMA-

approved drugs such as linaclotide and sildenafil, for anti-obesity pharmacotherapy. These cGMP-centered potential therapeutic opportunities encapsulate some of the main themes of the present review: new signaling pathways; new molecular targets; maximal safety; and synergy.

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Article highlights

- Obesity is a worldwide pandemic, with staggering health and economic costs.
- Existing strategies to combat obesity through lifestyle improvements have had limited success, and weight-loss medications have had serious safety risks, notably cardiovascular and psychiatric events.
- Current obesity studies are uncovering and characterizing new drug targets, including new signaling circuits and hormones regulating appetite and metabolism.
- To avoid the safety failures of many past weight-loss drugs, the new models and strategies incorporate recent advances in knowledge and technology, and aim for combinatorial or synergistic effects.
- The compensatory mechanisms driving weight regain following weight loss must be solved for anti-obesity therapy to achieve long-term success.
- Modulating cGMP signaling may represent an ideal goal for an anti-obesity pharmacotherapy.

Table 1

Current anti-obesity medication

Mechanism of action	Drug	
Appetite suppressant. Stimulates anorexic signaling in hypothalamus or dopamine receptor in the hippocampus. Sympathomimetic agents similar to norepinephrine with central nervous system (CNS) stimulatory activity.	Phentermine	FDA-approved in 1959
	Amphetamine	Off-label usage
	Dextroamphetamine	
	Methamphetamine	
Anorectic with appetite suppressive effect. Sympathomimetic amine with pharmacologic activity similar to amphetamine. Also stimulates CNS and elevates blood pressure.	Benzphetamine (Didrex)	FDA-approved in 1960
	Diethylpropion (Tenuate)	FDA-approved in 1959
	Phendimetrazine (Bontril, Adipost, Appecon etc.)	FDA-approved in 1982
	Dexfenfluramine (Redux)	FDA-approved in 1973 (Dexfenfluramine) and 1996 for fenfluramine. Both drugs were withdrawn from market in 1997 due to cardiovascular effects
	Fenfluramine (Pondimin, Ponderax, Adifax)	
Inhibits the neuronal uptake of dopamine, norepinephrine, and serotonin.	Bupropion (Wellbutrin, Zyban)	Off-label usage
Serotonin, dopamine and norepinephrine reuptake inhibitor (SNRI) that potentiates the neurotransmitter activity in the central nervous system (CNS).	Desvenlafaxine (Pristiq)	Off-label usage
	Sibutramine (Meridia)	FDA-approved in 1997, but withdrawn in 2010 due to cardiovascular effects
	Lorcaserin (Belviq)	FDA-approved in 2012
Selective cannabinoid-1 (CB-1) receptor antagonist.	Rimonabant (Acomplia, Bethin, Monaslim, Riobant, Slimona, Zimulti etc.)	EMA-approved drug in 2006, but withdrawn in 2008 due to possible suicide and psychiatric effects
The exact mechanism of action is unknown.	Topiramate (Topamax)	Off-label usage
Reversible inhibitor of intestinal lipases.	Orlistat (Xenical)	FDA-approved drug in 1999
Glucagon-like peptide-1 (GLP-1) receptor agonist.	Exenatide (Byetta, Bydureon)	Off-label usage
	Liraglutide (Victoza)	Off-label usage
Inhibitor of dipeptidylpeptidase-4.	Alogliptin (Nesina)	Off-label usage
	Saxagliptin (Onglyza)	Off-label usage
	Sitagliptin (Januvia)	Off-label usage
	Vildagliptin (Zomelis, Galvus)	Off-label usage
Amylin analog.	Pramlintide (Symlin)	Off-label usage
Cocktail drug.	Phentermine/topiramate (Osymia)	FDA-approved in 2012
	Amphetamine/Dextroamphetamine (Adderall)	Off-label usage

Table 2

Anti-obesity medication under development

Drug	Company	Mechanism of action	Status	Target
Central neuropeptide signaling				
ALB-127158	AMRI	MCH1 antagonist	Phase I completed	Melanin-concentrating hormone
BMS-830216	Bristol-Myers Squibb	MCH receptor antagonist	Phase II completed	
MK-0493	Merck	Selective MC4R agonist, increasing MC3/4R signaling	Phase II completed	
TM30339	7TM Pharma	Selective Y4-receptor agonist	IND was withdrawn	Melanocortin receptor
TTP435	TransTech Pharma	AgRP inhibitor, increasing MC3/4R signaling	Phase II completed	
MK-0557	Merck	Y5 receptor antagonist, NPY blocker	Phase II completed	
Obinipitide	7TM Pharma	Y4R agonist in DVC, Y2R agonist in arcuate nucleus	Phase II	
PYY 3-36	Merck/Pfizer/Nastech	Y4R agonist in DVC, Y2R agonist in arcuate nucleus	Phase II completed	
PYY 3-36/SNAC	Emisphere	Y4R agonist in DVC, Y2R agonist in arcuate nucleus	Phase I/II	NPY
Velneperit (S-2367)	Shionogi USA	Y5 receptor antagonist, NPY blocker	Phase II completed	
Monoamine neurotransmission				
Contrave (bupropion/naltrexone)	Orexigen	Norepinephrine/dopamine reuptake inhibitor	Safety study requested in Feb 2011 due to cardiovascular risk	Dopamine/norepinephrine/serotonin
GSK598809	GlaxoSmithKline	Dopamine (D3) antagonist	Phase I completed	
Empatic™ (zonisamide SR/bupropion SR)	Orexigen	Norepinephrine/dopamine reuptake inhibitor GABA receptor activator	Phase II completed	
Tesofensine (NS2330)	NeuroSearch	Serotonin/norepinephrine/dopamine reuptake inhibitor	Phase II	
A-331440	Abbott Laboratories	Non-imidazole histamine H3 receptor antagonist	Pre-clinical	Histamine
HPP404	TransTech Pharma	Selective H3 receptor antagonist	Phase II active, but not recruiting	
SCH-497079	Schering-Plough	Histamine receptor antagonist	Phase II completed	
Intestinal peptide hormone signaling				
GI 181771X	GlaxoSmithKline	CCK-A agonist, mimicking the effect of CCK	Terminated	CCK
AEZS-123	AEterna Zentaris	Ghrelin receptor antagonist	Pre-clinical	
CYT009-GhrQb	Cytos	First-generation ghrelin vaccine, bind and inhibit ghrelin	Terminated	Ghrelin
Spiegelmer® (NOX-B11)	Pfizer/Noxxon	Bind and inhibit ghrelin	Phase II	

Drug	Company	Mechanism of action	Status	Target
NN9024	Novo Nordisk	GLP1R agonist, GLP-1 mimicking	Phase I completed	GLP-1
Byetta® (exenatide)	Amylin	GLP1R agonist, GLP-1 mimicking	Phase III	
Qxynomodulin (OXY-RPEG)	Prolor	GLP1R agonist, OXM mimicking	Phase I recruiting	OXM
TKS1225	Thiakis/Wyeth/Pfizer	GLP1R agonist, OXM mimicking	Phase I	
Pancreatic hormone signaling				
PP1420	Wellcome Trust	Pancreatic polypeptide analog	Phase I completed	PP
Davalintide (AC2307)	Amylin	Amylin mimicking	Phase II	Amylin
Adipose tissue hormone signaling				
Metreleptin	Amylin/Takeda	Leptin receptor agonist	Phase III recruiting	Leptin
Inhibition of lipase				
Cerilistat (ATL-962)	Alizyme/Takeda/Norgine	Pancreatic lipase inhibitor, inhibiting intestinal lipid absorption	Phase III completed	Pancreatic lipase
Other				
Fumagillin	Zafgen	Methionine aminopeptidase 2 inhibitor	Pre-clinical	MetAP2
ZGN-433	Zafgen	Methionine aminopeptidase 2 inhibitor	Phase I completed	
GW869682	GlaxoSmithKline	excreting glucose in the urine by SGLT2 inhibition	Phase II completed	
Invokona™ (canagliflozin, JN1-28431754)	Johnson & Johnson	excreting glucose in the urine by SGLT2 inhibition	Recommended for approval by FDA subcommittee	Sodium dependent glucose Sodium-dependent glucose transporter
AZD7687	AstraZeneca	Diglyceride acyltransferase inhibitor, inhibiting triglyceride synthesis	Phase I completed	DGAT1
AZD4017	AstraZeneca	11β-HSD1 inhibitor	Phase IIa recruiting	
AZD8329	AstraZeneca	11β-HSD1 inhibitor	Phase I completed	11β-HSD1
INCB13739	Incyte	11β-HSD1 inhibitor	Phase I completed	