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Obesity pharmacotherapy: What is next?

Francheska Colon-Gonzalez^{1,‡}, Gilbert W. Kim¹, Jieru E. Lin¹, Michael A. Valentino¹, and Scott A. Waldman¹

¹Department of Pharmacology and Experimental Therapeutics, Thomas Jefferson University, Philadelphia, PA

Abstract

The increase in obesity in the United States and around the world in the last decade is overwhelming. The number of overweight adults in the world surpassed 1 billion in 2008. Health hazards associated with obesity are serious and include heart disease, sleep apnea, diabetes, and cancer. Although lifestyle modifications are the most straightforward way to control weight, a large portion of the population may not be able to rely on this modality alone. Thus, the development of anti-obesity therapeutics represents a major unmet medical need. Historically, anti-obesity pharmacotherapies have been unsafe and minimally efficacious. A better understanding of the biology of appetite and metabolism provides an opportunity to develop drugs that may offer safer and more effective alternatives for weight management. This review discusses drugs that are currently on the market and in development as anti-obesity therapeutics based on their target and mechanism of action. It should serve as a roadmap to establish expectations for the near future for anti-obesity drug development.

Keywords

obesity; anti-obesity drugs; appetite; metabolism

1. Introduction

Obesity and excess weight are rapidly growing health hazards in the United States and around the world. In 2008, 33.8% of US adults 20 years and older were obese (body mass

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[‡]Corresponding Author: Francheska Colon-Gonzalez, Ph.D., 1020 Locust St., JAH 349, Philadelphia, PA 19107, Tel: 215-955-0054, Tel: 215-955-5964, Fax: 215-955-7006, Francheska.Colon-Gonzalez@jefferson.edu.

Gilbert W. Kim, B.S., B.S., 1020 Locust St., JAH 349, Philadelphia, PA 19107, Tel: 215-955-0054, Tel: 215-955-5964, Fax: 215-955-7006, Gilbert.Kim@jefferson.edu

Jieru E. Lin, B.Pharm, M.S., Ph.D., 1020 Locust St., JAH 349, Philadelphia, PA 19107, Tel: 215-955-0054, Tel: 215-955-5964, Fax: 215-955-7006, egeria.lin@hotmail.com

Michael A. Valentino, B.S., 1020 Locust St., JAH 349, Philadelphia, PA 19107, Tel: 215-955-0054, Tel: 215-955-5964, Fax: 215-955-7006, Michael.Valentino@jefferson.edu

Scott A. Waldman, M.D., Ph.D., Department of Pharmacology and Experimental Therapeutics, Thomas Jefferson University, 132 S. 10th St., 1170 Main, Philadelphia, Pennsylvania 19107, Tel: 215-955-6086, Fax: 215-955-5681, Scott.Waldman@jefferson.edu

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index $> 30 \text{ kg/m}^2$) and another 34.2% were overweight (body mass index $> 25 \text{ kg/m}^2$) (Flegal et al., 2010). Globally, 1.5 billion adults 20 years and older were overweight, with nearly 500 million of them being obese (WHO, 2011). Even more alarming is the rapid increase in childhood obesity. In 2010, nearly 43 million children under the age of 5 were overweight worldwide. Obesity is complicated by its associated comorbidities, which include cancer, diabetes, heart disease, and obstructive sleep apnea, among others. The prevalence of obesity and its related diseases are threatening the health systems of both wealthy and poor countries. In 2008, national Medicare costs related to obesity were estimated at \$147 billion (CDC, 2011).

The rising concern over obesity as a global health hazard is relatively recent and it has outpaced the pharmaceutical industry's ability to develop new and safe drugs. Despite the increasing need for new anti-obesity therapeutics, the food and drug administration (FDA) has not approved a new anti-obesity drug since orlistat in 1999. This, in part, reflects the lack of new approaches to drug development in the past years and the efficacy and safety requirements set by the FDA. In order to win approval, a 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 (FDA, 2007). The drug must also be safe for use in the intended population. The obese population is a mixed pool of relatively healthy to very sick individuals. The inherent complexity of this population, and the fact that an obesity drug could represent lifelong therapy, appropriately raises safety concerns for new drugs. This concern was evident in the recent rejection of proposed weight-loss drugs Contrave, Qnexa, and lorcaserin. Discoveries of new molecular targets that control appetite, lipogenesis, and metabolism are anticipated to lead to a new wave of targeted pharmacotherapies that feature higher efficacies and improved safety profiles for the prevention and treatment of obesity

2. History of obesity pharmacotherapy

The history of modern weight-loss drug therapy is replete with safety concerns since its inception in the late nineteenth century. In the 1890s, sheep thyroid extract was found to increase metabolic rate and induce weight loss in euthyroid patients, but was also responsible for an increase in cardiac arrhythmias and cardiac arrest (Bhasin et al., 1981). The drug 2,4-dinitrophenol was introduced to the market in the 1930s after it was observed that workers who handled the compound achieved a marked weight loss. It became a popular weight-loss drug but was discontinued when it was revealed to cause agranulocytosis, cataracts, dermatitis, and fatal hyperthermia (1935).

In 1947, amphetamine was approved for the treatment of obesity in the US but it was soon shown to have addictive properties. In the 1950s, other related sympathomimetic agents, phentermine and diethylpropion, were introduced and their use was widespread. During the 1940s-1960s, amphetamines were promoted in "rainbow" pill regimens that also included digitalis, diuretics, laxatives, and thyroid hormone, with barbiturates to counteract the nervousness and hyperactivity induced by the stimulants. Their association with myocardial toxicity and sudden death led to the decline in the use of these pill regimens (Asher, 1972). In the late 1960s, Aminorex, a drug with similar properties to amphetamine, was introduced

in Europe. Tragically, patients using the drug suffered from chronic pulmonary hypertension, with ~50% mortality among affected individuals (Gurtner, 1985).

During the 1980s-1990s, fenfluramine, another compound structurally related to amphetamine that stimulates the release of serotonin and inhibits the reuptake of presynaptic serotonin, was widely prescribed. In 1992, fenfluramine was combined with phentermine and marketed as the popular drug Fen-Phen. Although fenfluramine had been in use for many years, it was not until Fen-Phen became widely used that it was recognized that users were at risk for developing pulmonary hypertension and valvular heart disease. This observation led to the withdrawal of fenfluramine and its derivative, dexfenfluramine, from the market in 1997 (Connolly et al., 1997).

The sympathomimetic amine phenylpropanolamine (PPA) was commonly added to many cough and cold remedies and appetite suppressants since the 1970s, though its anti-obesity use was not licensed. In 2000, an association between the use of PPA and the occurrence of intracranial bleeding and strokes was demonstrated (Kernan et al., 2000). Following this report, the FDA issued a health advisory report requesting that all companies discontinue marketing products containing PPA, and in 2005 the FDA removed it from all over-the-counter products (FDA, 2005). Notably, PPA is still available in prescription decongestants in Europe and its use is completely derestricted in the United Kingdom. Other dietary supplements containing ephedra alkaloids were banned from sale by the FDA in 2004 due to reports of adverse effects such as heart attacks, hypertension, palpitations, strokes, and sudden death (Haller and Benowitz, 2000).

In 2008, reports of increased depression and suicide led an FDA panel to recommend that Rimonabant, a potent, selective endocannabinoid (CB₁ receptor) inverse agonist, be denied approval despite promising results in clinical trials. The European Medicines Agency also suspended its approval in 2008. These actions triggered Sanofi-Aventis to terminate studies on Rimonabant and discontinue development of other CB₁ antagonists. Sibutramine, a centrally-acting serotonin-norepinephrine reuptake inhibitor structurally related to amphetamines, was introduced in the US market in 1997. It was, however, removed from both the UK and US markets in 2010 due to increased cardiovascular risks.

Currently, orlistat is the only drug FDA-approved for long-term obesity management. It is sold with prescription under the name of Xenical (Roche Pharmaceuticals) and over-the-counter as Alli (GlaxoSmithKline). Orlistat is a lipase inhibitor that reduces intestinal fat absorption and has undesirable gastrointestinal side effects such as steatorrhea. In addition, reports of severe liver injuries prompted the FDA to issue a warning on May 2010. More recently, in April 2011, a review of patients taking orlistat in Ontario, Canada over a seven-year period revealed a 2% increase in acute kidney injuries within one year of starting the drug (Weir et al., 2011). In the same month, the consumer advocacy group and drug safety watchdog Public Citizen sent a letter to the FDA requesting the ban of orlistat, citing liver toxicity as well as evidence from the FDA adverse-reaction files that included 47 cases of acute pancreatitis and 73 cases of kidney stones (Public-Citizen, 2011). On the same day, GlaxoSmithKline announced that it plans 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,

putting in doubt the future of this product (GSK, 2011). In Table 1, we list the medications that are currently used to induce weight loss, including those used off-label.

This history of weight-loss pharmacotherapy highlights the need for new, safer, and more effective approaches to treat and prevent obesity. In the next section we discuss the drugs that are currently under development based on their target and mechanism of action.

3. Obesity therapies under development

3.1. Modulation of central neuropeptide signaling

The primary neural site for appetite regulation by peripheral signaling hormones is the arcuate nucleus (ARC) of the hypothalamus. 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). Projections of these neurons to the dorsomedial nucleus, paraventricular nucleus, lateral hypothalamus, and prefrontal area relay the signals to secondary neurons that then process and integrate the information.

NPY is a potent orexigenic neuropeptide. Activation of the Y1 and Y5 G protein-coupled receptors (GPCRs) mediates NPY-induced feeding (Larhammar, 1996). Inhibition of this signaling reduces food intake and body weight in mice (Kanatani et al., 2000; Mashiko et al., 2009). In 2010, Merck abandoned the development of the NPY receptor antagonist MK-0557 after results from a year-long study produced a statistically significant but not clinically meaningful (less than 3 kg) weight loss (Erondur et al., 2006). However, another Y5 receptor inhibitor, S-2367 (Velnepert; Shionogi), induced significant weight loss over the course of one year in two double-blind studies (Shionogi, 2009). Obese patients taking 800 mg daily in combination with a reduced-calorie diet had 5% or greater weight loss when compared to placebo. In addition, S-2367 was also effective in reducing waist circumference and improving lipid panels. S-2367 was well-tolerated over the course of the studies and continues to be studied in phase II clinical trials. An inhibitor of AgRP (TTP435, TransTech Pharma) is also in phase II trials (TransTech-Pharma, 2011).

Melanin-concentrating hormone (MCH) is a potent orexigenic neuropeptide 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 (AMRI, 2011; BMS, 2011). Cleavage of POMC yields several hormones, including -melanocyte stimulating hormone (-MSH). Melanocortins induce their anorexigenic effects through activation of the melanocortin 3 (MC3R) and melanocortin 4 (MC4R) receptors. Although an agonist of MC4R, MK-0493 (Merck), showed promising results in rodent models of diet-induced obesity, it failed to demonstrate statistically significant results in phase II clinical trials (Krishna et al., 2009). A small peptide agonist with higher specificity for MC4R (RM-493; Rhythm) has shown promising results in preclinical testing (Rhythm, 2011). Mutations in MC4R represent a genetic basis of obesity. 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 (Tao, 2010). MC4R is, however, another anti-obesity target that may raise significant safety concerns due to the role of melanocortins in cardiovascular and sexual function (Wikberg and Mutulis, 2008).

3.2. Modulation of monoamine neurotransmission

3.2.1. Dopamine, norepinephrine, and serotonin—Pharmacotherapy that targets monoamine neurotransmitters, such as dopamine, norepinephrine, and serotonin, has been effective in driving weight loss in patients (Schwartz et al., 2000). However, due to the manifold neuronal functions mediated by these neurotransmitters, use of such drugs poses risks for addiction, cardiovascular events, hypertension, and tolerance (Sargent and Moore, 2009).

A triple monoamine reuptake inhibitor, tesofensine (NeuroSearch), has produced promising results in phase II clinical trials. Tesofensine was originally developed for the treatment of 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 (Astrup et al., 2008). 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 (Sjodin et al., 2010). 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, but sought a partner to help finance the continuing development and commercialization costs (NeuroSearch, 2011).

Combination therapy targeting monoamine neurotransmitters is also under development. Contrave (Orexigen) combines 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 (Greenway et al., 2009). In phase III clinical trials, Contrave demonstrated that patients on a diet and exercise program achieved greater weight loss over 56 weeks with bupropion/naltrexone (6.1 kg) than with placebo (1.4 kg) (Orexigen, 2010). Although an FDA sub-panel recommended Contrave for approval as an anti-obesity treatment, the FDA ultimately rejected Contrave for anti-obesity treatment, and requested a large cardiovascular risk trial to address potential side effects before it could approve the drug (Orexigen, 2011). Orexigen plans to appeal the decision after failing to reach an agreement with the FDA on how to conduct such a trial. Orexigen also 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 (Orexigen, 2009). At 24 weeks, patients had shown no evidence of plateau, which suggested that greater weight loss could be achieved in a year-long trial.

Another combination drug, Qnexa (Vivus), which combines the antiepileptic topiramate and the norepinephrine reuptake inhibitor phentermine, was rejected by the FDA as a weight-loss drug due to concerns over adverse effects, including birth defects, heart palpitations, memory lapses, and suicidal thoughts (Vivus, 2010).

Serotonin activates 5HT_{2C} receptors to regulate feeding behavior and energy balance (Nonogaki et al., 1998). A selective 5HT_{2C} agonist, lorcaserin (ADP-356; Arena), demonstrated efficacy in generating weight loss in phase II/III testing. However, the FDA denied approval for lorcaserin due to the risk of tumor formation in rats as well as its marginal effectiveness in driving weight loss (Arena, 2010).

Dopamine regulates the motivation for food intake. Indeed, recent studies revealed that dopamine levels spike in response to food stimuli in binge eaters (Wang et al., 2011). Dopamine receptor inhibition, then, represents a potential 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.

3.2.2. Histamine—Central histamine signaling plays a role in appetite regulation, and modulation of histamine receptor signaling has produced body weight and food intake changes in obese mice (Masaki et al., 2003; Yoshimoto et al., 2006). 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. Antagonists targeting the H₃-histamine receptor have, in fact, been a focus for weight-loss drug development since 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 (Hancock et al., 2004). Another selective H₃-receptor antagonist, HPP404 (TransTechPharma), is in phase I clinical trials. Schering-Plough completed a phase II clinical trial of its H₃-receptor antagonist SCH-497079.

3.3. Modulation of intestinal peptide signaling

3.3.1. Cholecystokinin (CCK)—Cholecystokinin is an intestinal peptide secreted by the I cells in the duodenum and jejunum in response to foods high in fat and protein (Crawley and Corwin, 1994). It aids in digestion and also serves as a neurotransmitter in the CNS (Moran, 2000). 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 (Moran et al., 1997; Moran and Bi, 2006; Moran et al., 1988). In humans, the CCK-A receptor antagonist, loxiglumide,

induces higher caloric intake (Beglinger et al., 2001). However, CCK effects on weight reduction are limited due to tolerance after chronic administration in animals (Crawley and Beinfeld, 1983; Lukaszewski and Praissman, 1988). Intermittent CCK administration reduces the size but increases the frequency of meals (West et al., 1984). GlaxoSmithKline terminated development of the selective CCK-A agonist GI 181771X after it failed to induce weight loss in phase II trials (Fong, 2005). In addition, chronic CCK administration in animals induced pancreatitis, raising safety concerns for the development of drugs in this class (Pandol et al., 1999; Plusczyk et al., 1997). Notably, however, CCK potentiates appetite and weight reduction by leptin (Matson and Ritter, 1999), which suggests that combination therapy may hold promise.

3.3.2. Glucagon-like peptide 1 (GLP-1)—Glucagon-like peptide 1 (GLP-1), a product of the preproglucagon gene, is generated by enteroendocrine L cells in the ileum and proximal colon (Drucker, 2006). Secretion of GLP-1 is induced by meal ingestion. GLP-1 functions include increasing insulin secretion, suppression of glucagon, reduction of gastric emptying, and decreasing 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 (Drucker, 2006). Administration of GLP-1 in animals and humans induces satiety and weight loss (Flint et al., 1998; Meeran et al., 1999; Naslund et al., 2004; Turton et al., 1996). However, its utility is limited by rapid proteolysis by dipeptidyl peptidase IV (DPP-IV) (Mentlein et al., 1993).

To overcome this issue, the proteolysis-resistant GLP-1 analogs liraglutide (Victoza; Novo Nordisk) and exenatide (Byetta; Amylin/Eli Lilly) have been developed and 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 (Amori et al., 2007; Fakhoury et al., 2010; Phung et al., 2010; Pratley, 2008). 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 (Amori et al., 2007). 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 treatment.

A long-acting release formulation of exenatide (exenatide-LAR; Amylin), which is injected once weekly, has been developed to overcome the need for daily injections with the original drugs. In a 15-week trial in diabetic patients, exenatide-LAR was shown to improve body weight. After two years of weekly exenatide-LAR treatment, patients observed an average reduction in weight 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. A longacting 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 (Emisphere, 2011). In a study of 12 healthy male subjects, the oral GLP-1 analog (2.0 mg) produced a significant reduction ($13.6 \pm 3.6\%$) of total food intake, but only a weak effect

was seen on hunger and satiety (Steinert et al., 2010). Interestingly, although DPP-IV inhibitors, such as vildagliptin (Novartis), saxagliptin (Onglyza; Astra Zeneca) and sitagliptin (Januvia; Merck), have been developed, these have been shown to have little or no effect on weight loss (Amori et al., 2007; Fakhoury et al., 2010; Phung et al., 2010; Pratley, 2008).

3.3.3. Oxyntomodulin (OXM)—Oxyntomodulin is a potent anorexigenic peptide also produced from the processing of preproglucagon. OXM is secreted postprandially along with GLP-1 by the L cells of the colon and has minimal incretin function. It is thought that OXM mediates its anorectic effects via activation of central GLP-1Rs and as well as stimulation of POMC neurons in the ARC. In humans, IV infusion of OXM suppressed appetite and feeding and increased energy expenditure (Batterham et al., 2003a; Wynne et al., 2006). However, the need for continuous infusions of OXM was a substantial limitation for 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 OXY-RPEG (PROLOR-Biotech, 2011). This technology seems to increase not only the half-life of OXM but also its potency. In a study using animal models, OXY-RPEG injected either once or twice weekly demonstrated significantly greater weight loss, reduction of food intake, and duration of weight loss activity when compared to OXM injected twice daily (PROLOR-Biotech, 2011).

3.3.4. Peptide YY (PYY)—PYY is a potent anorexigenic peptide of the pancreatic polypeptide family, which binds to the GPCRs Y1-Y6 (Larhammar, 1996). It is produced in the gut by the L cells of the terminal ileum and colon and secreted to the circulation in response to a meal (Adrian et al., 1985). PYY stimulates gastrointestinal absorption of fluids and electrolytes (Liu et al., 1996), reduces gastric and pancreatic secretions, and delays gastric emptying (Adrian et al., 1985). The common circulating form, PYY₃₋₃₆, has high affinity for the Y2 receptors. It is believed that this peptide suppresses appetite by activating pre-synaptic Y2R in the ARC, which inhibits the activity of orexigenic NPY/AgRP neurons. Interestingly, obese humans and rodents have lower circulating levels of postprandial PYY compared to lean controls (le Roux et al., 2006). Following bariatric surgery, plasma levels of PYY rise back to normal, which contributes to the efficacy of bariatric surgery in producing long-term weight loss. The idea that obesity causes a deficiency of PYY, rather than resistance against PYY, highlights its potential as a therapeutic target. In studies with healthy subjects, continuous infusion of PYY reduced hunger and caloric intake by 36% (Batterham et al., 2002), and obese patients behaved similarly (Batterham et al., 2003a). PYY infusion resulted in a dose-dependent reduction in food consumption, with a maximum inhibition of 35% (Degen et al., 2005).

As with other peptides, technologies are in development to create stable forms of PYY 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 (Ortiz et al., 2007). However, an intranasal formulation of PYY

(Nastech/Merck) failed to induce weight loss in humans (Gantz et al., 2007). Utilizing the SNAC carrier technology (Emisphere Technologies), a PYY₃₋₃₆ oral formulation was developed. This oral formulation was rapidly absorbed by the GI tract, but caused a non-significant reduction of energy intake (12.0 + 6.7%, vs placebo) and only weak effects on hunger and satiety in healthy human subjects (Steinert et al., 2010). Interestingly, a synergistic effect in both energy intake and fullness was seen when co-administered with GLP-1, suggesting the potential for combination therapy (Steinert et al., 2010). Treatment with either PYY₃₋₃₆ or GLP-1 alone or in combination caused decreases in plasma levels of the orexigenic peptide ghrelin during meal consumption (Steinert et al., 2010). A therapeutic limitation of PYY is that it produces nausea and vomiting in a dose-dependent manner (Degen et al., 2005; Gantz et al., 2007; Steinert et al., 2010).

3.3.5. Ghrelin—Ghrelin, the only known circulating orexigenic hormone, is cleaved from its precursor prepro-ghrelin. It is produced mainly in the gastric fundus. Its effects on obesity are related to increasing appetite and food intake while reducing energy expenditure. In addition to its effects as an orexigenic peptide, ghrelin has been reported to stimulate the release of growth hormone (GH) by activating the growth hormone secretagogue receptor (GHS-R) (Kojima et al., 1999). However, its physiological relevance on GH release is unclear (Sun et al., 2003). Ghrelin regulates hunger and feeding mainly by activating NPY/AgRP neurons in the ARC, although vagal stimulation and other CNS sites expressing GHS-R, including the dorsal raphe nucleus, hippocampus, and mesolimbic reward pathway, also seem to be involved (Carlini et al., 2004; Date et al., 2002; Naleid et al., 2005). Long-term energy homeostasis is regulated by ghrelin. Circulating levels of ghrelin are reduced in obese patients but exaggerated in anorexic patients. A decline in ghrelin levels is correlated with weight gain but levels increase substantially with diet-induced weight loss, which may contribute to the difficulty in maintaining the weight loss (Beck and Richy, 2009; Otto et al., 2001; Tolle et al., 2003; Tschop et al., 2001). The success of bariatric surgery has been correlated to inhibition of this diet-induced rise in ghrelin levels (Karra et al., 2010).

Blocking ghrelin's action has been a focus of anti-obesity drug development programs. Neutralization of ghrelin was investigated with a first-generation ghrelin vaccine, CYT009-GhrQb (Cytos). Although patients exhibited a strong ghrelin antibody response, they did not lose weight, which resulted in the discontinuation of this vaccine (Cytos, 2006). Several second-generation vaccines have been developed and shown to decrease feeding, adiposity, and body weight in rodents (Andrade S, 2011; Zorrilla et al., 2006). A ghrelin-neutralizing RNA Spiegelmer, NOX-B11 (NOXXON Pharma AG), which binds to and inactivates ghrelin, blocked the orexigenic activity of exogenous ghrelin administration but failed to alter food intake in rats (Moran and Dailey, 2009). Ghrelin antagonists from Elixir Pharmaceuticals/Novartis and AEterna Zentaris (AEZS-123) are in preclinical testing (AEterna-Zentaris, 2011). 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 (Yang et al., 2008).

3.4. Modulation of pancreatic hormone signaling

3.4.1. Pancreatic polypeptide (PP)—Pancreatic polypeptide (PP) is a satiety peptide that possibly originated from duplication of the *PYY gene* (Hort et al., 1995). PP is primarily produced in the pancreas and binds with highest affinity to Y4 and Y5 receptors (Larhammar, 1996). Circulating levels of PP rise after meal ingestion proportionally to caloric intake and remain elevated for up to six hours (Adrian et al., 1976). Peripheral hormones, including ghrelin, also induce PP secretion (Chaudhri et al., 2006). PP's effect on appetite is mediated mainly through signaling in the area postrema (AP) of the DVC, which induces changes in levels of hypothalamic peptides (Asakawa et al., 2003). Peripheral administration of PP has been demonstrated to decrease appetite and weight gain in rodents (Asakawa et al., 2003; Malaisse-Lagae et al., 1977). Plasma levels of PP are lower in obese patients (Reinehr et al., 2006), while PP responses are exaggerated in patients with anorexia nervosa (Fujimoto et al., 1997). IV infusion of PP (10 pmol/kg/min) in healthy subjects reduced appetite and caloric intake by 22%, and proved effective over 24 hours (Batterham et al., 2003b). Since PP has a short half-life (Adrian et al., 1978), 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, Obinepitide (7TM Pharma), and a selective Y4-receptor agonist, TM30339 (7TM Pharma), are in phase I/II clinical trials (7TM-Pharma, 2011a, b).

3.4.2. Amylin—Amylin, or islet amyloid polypeptide (IAPP), is secreted along with insulin by pancreatic β -cells (Pittner et al., 1994), and type 1 diabetics are deficient in both hormones. Fasting plasma levels of amylin are low, and increase after meal consumption (Koda et al., 1992; Koda JE, 1995). Amylin acts not only to regulate glucose levels in synergy with insulin, but also drives anorectic functions. Amylin receptors are expressed in certain CNS regions, including the AP of the DVC (Young A, 2000), and vagal signaling is critical to amylin-mediated appetite suppression (Edwards GL, 1998; Jodka C, 1996; Lutz et al., 2001). ICV administration reduced food intake in rodents while constant infusion over 10 days reduced feeding and adiposity (Rushing et al., 2000). Pramlintide, a synthetic amylin analog that is approved for the treatment of diabetes (Symlin; Amylin) (Edelman and Weyer, 2002), is similar to amylin both pharmacokinetically and pharmacodynamically (Young A, 1996). Body weight reductions were observed in both type 1 and 2 diabetics treated with pramlintide (Hollander et al., 2003; Ratner et al., 2002; Whitehouse et al., 2002). A pooled, *post-hoc* analysis in type 2 diabetic subjects demonstrated that pramlintide, at 120 μ g b.i.d. or 150 μ g q.d., induced an average weight loss of 2.6 kg over 52 weeks of therapy (Maggs et al., 2003). Adverse effects were minimal and consisted of a transient increase in mild-to-moderate nausea and headache (Hollander et al., 2003; Maggs et al., 2003; Ratner et al., 2002; Whitehouse et al., 2002). Davalintide, Amylin Pharmaceutical's second-generation amylin analog that has enhanced amylin pharmacologic properties, is in phase II clinical trials.

3.5. Modulation of adipose tissue hormone signaling

3.5.1. Leptin—Leptin is an adipose tissue-derived hormone that was called the “obese gene” (*ob*) after mice harboring mutations developed morbid obesity (Ingalls et al., 1996).

Humans with congenital leptin deficiency show early-onset obesity that is treated with leptin replacement therapy (Farooqi and O'Rahilly, 2005; Montague et al., 1997). Activated leptin receptors in the hypothalamus increase POMC expression and stimulate POMC/CART signaling (Myers, 2004), while suppressing AgRP expression and inhibiting NPY/AgRP signaling in the ARC (Schwartz et al., 1996; Schwartz et al., 1997; Stephens et al., 1995). However, leptin receptor resistance usually manifests in obese patients, who exhibit high circulating levels of the hormone (Considine et al., 1996). Circulating levels of leptin are correlated with degree of adiposity (Considine et al., 1996) and feeding state (Ahima et al., 1996). Thus, leptin as a therapeutic target has proved disappointing due to receptor resistance (Ozcan et al., 2009).

However, treatment with amylin restores leptin receptor signaling in the hypothalamus in the context of obesity (Roth et al., 2008). Amylin and leptin seem to act in synergy to reduce appetite and weight in rats. Synergy with leptin has not been detected with other peptides. Importantly, this resensitization translates to humans. Overweight and obese patients treated with twice daily injections of pramlintide and metreleptin (a synthetic leptin analog) achieved higher weight loss than those on monotherapy (Ravussin et al., 2009). Combination therapy also resulted in continued weight loss compared to a plateau reached by the placebo group. The most common adverse events were injection-site events and mild-to-moderate nausea, which decreased over time. In a follow-up, phase II, dose-ranging study, overweight and obese individuals were treated with combination therapy b.i.d. At the highest doses tested (pramlintide 360 mcg, metreleptin 5mg), combination therapy patients lost ~11% of body weight, which was significantly greater than patients receiving either agent alone or placebo at ~5.0% and 1.8% respectively (Amylin, 2009). Patients that continued treatment in a 52-week extension of this trial demonstrated sustained weight loss while those receiving placebo regained all their lost weight (Amylin, 2010). 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 (Amylin, 2011).

3.6. Inhibition of lipases

Pancreatic lipase acts to hydrolyze triglycerides in the diet into more absorbable free fatty acids. Lipase inhibitor treatment 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. The undesirable gastrointestinal side effects such as steatorrhea that are associated with this first-generation drug have hampered its success in the market. A second-generation lipase inhibitor, cetilistat (Alizyme/Takeda) is under development and is thought to have a better 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 (Kopelman et al., 2007). Cetilistat is currently in phase III clinical trials in Japan.

3.7. Other targets

3.7.1. Methionine aminopeptidase 2 (MetAP2)—ZGN-433 (Zafgen) is an inhibitor of methionine aminopeptidase 2 (MetAP2). MetAP2 is an enzyme critical to post-translational

processing and protein synthesis. Initially, ZGN-433 was developed as an anti-cancer agent because MetAP2 plays a role in tumor vascularization and metastasis (Datta, 2009). However, preclinical data suggested possible efficacy in body weight control. Although the precise mechanism of action for ZGN-433 in obesity treatment is not clear, it is believed that MetAP2 inhibitors work by re-establishing balance in fat metabolism, leading to body weight reduction and improved glucose tolerance. Indeed, oral gavage with fumagillin, another MetAP2 inhibitor, reduced adipose tissue formation in diet-induced obese mice (Lijnen et al.). In a phase Ib study with severely obese patients (body mass index = 32–35 kg/m²), ZGN-433 (0.9 mg/m²) reduced body weight by a median value of 1 kg per week and 3.1% over 26 days relative to placebo controls (Zafgen, 2011). ZGN-433 was administered by intravenous infusion twice weekly over a four-week treatment period for a total of eight doses at three different dose levels (0.22, 0.65, and 1.96 mg per administration). A reduction in hunger and meaningful changes in lipid parameters were observed. The drug was well-tolerated over the course of the experiment. Zafgen plans to initiate phase II studies in 2011.

3.7.2. Diglyceride acyltransferase (DGAT)—Diglyceride acyltransferase (DGAT) catalyzes the final reaction of triglyceride synthesis. Because of DGAT's role in adipose tissue formation, its inhibition has been explored as a possible way to treat obesity. Indeed, mice lacking DGAT expression are lean and resistant to diet-induced obesity (Smith et al., 2000). AZD7687 (Astra Zeneca) is a DGAT inhibitor currently in phase I clinical trials for obesity and diabetes therapy. Takeda Pharmaceuticals demonstrated that their DGAT inhibitor stimulated lipid metabolism in muscle and induced weight reduction in mouse models of obesity (Yamamoto et al., 2011).

3.7.3. 11 β -hydroxysteroid dehydrogenases (11 β -HSDs)—11 β -hydroxysteroid dehydrogenases (11 β -HSDs) are enzymes implicated in a number of diseases, including obesity, type 2 diabetes and hypertension. They play an important role in the interconversion of glucocorticoids between active cortisol and inactive cortisone. Two isoforms have been identified: 11 β -HSD1 and 11 β -HSD2. These 11 β -HSDs play a major role in the modulation of local cortisol levels and the access of active steroid to its receptors in target tissues. Excess glucocorticoids produce visceral obesity and diabetes. 11 β -HSD1 is present in liver and adipose tissue. Its activity can be altered by factors such as glucocorticoids, stress, sex steroids, growth hormone, cytokines and PPAR agonists. The levels of 11 β -HSD1 are markedly increased in adipose tissue of obese individuals. Transgenic mice with increased 11 β -HSD1 activity have an excess of visceral fat and are insulin resistant, diabetic, and dyslipidemic (Masuzaki et al., 2001). This finding has launched the 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).

4. Conclusion

The main hurdle to approve new drugs into the market seems to be balancing the risk-benefit ratio. The history of unsafe weight-loss drugs is extensive, as is the list of comorbidities associated with obesity. Clearly, establishing safety is paramount to responsible anti-obesity

drug development. The pharmaceutical industry and the FDA must work together to define an appropriate risk-benefit ratio that should guide future drug development programs.

The industry is focused on developing drugs that target new pathways, with the hope that these will be more effective and have far fewer undesirable side effects than previous drugs. As we advance our understanding of the biology of appetite regulation and metabolism, it is certainly possible that safe and effective drugs can be developed. Moreover, the development of new technologies is promising. Pegylation technology, for example, stabilizes the satiety hormone oxyntomodulin to not only reduce the injection frequency from twice-to-thrice daily to once-to-twice weekly, but also improve its potency.

The scale of the obesity epidemic makes it imperative that the pharmaceutical industry and the FDA continue their collaborative efforts to bring safe and effective drugs to patients. Fortunately, the market's recognition of the potential profit from this unmet need continues to drive research and investment in this field. As discussed in this review, an array of potential new drugs, either alone or in combination, may provide the millions of obese patients a tool to help reach a healthy weight.

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Biographies

Francheska Colon-Gonzalez received her PhD in Pharmacology from the University of Pennsylvania. Her graduate work focused on cell signaling and molecular biology and was funded by an NCI minority supplement. Currently, she is a Clinical Pharmacology Fellow at Thomas Jefferson University. There, she is receiving training in clinical research as well as continuing her basic research training in the Waldman laboratory. She was awarded a PhRMA Foundation Post-Doctoral Fellowship to support her research investigating the molecular mechanisms linking obesity and colon cancer. Her long-term goal is to have a career in drug development and clinical research.

Gilbert W. Kim is an MD/PhD student in the Molecular Pharmacology and Structural Biology Program at Thomas Jefferson University in Philadelphia, PA. He is conducting his doctoral thesis research with Scott A. Waldman, MD, PhD, in the Department of Pharmacology and Experimental Therapeutics. He earned a BS in biology and a BS in literature from the Massachusetts Institute of Technology in Cambridge, MA. He was born in Los Angeles, CA.

Dr. Jieru E. Lin holds a PhD in Molecular Pharmacology and Structural Biology from Thomas Jefferson University, Philadelphia, PA. She received her Pharmacy degree from the National Taiwan University and is a licensed pharmacist in Taiwan. Her doctoral and postdoctoral training is focused on colorectal tumorigenesis, tumor metabolism, and obesity. Among these areas, she has published multiple peer-reviewed articles. Her long term goal is to link these areas of interests by connecting obesity and colorectal tumorigenesis.

Michael Valentino is pursuing a career as a physician-scientist as a candidate in the MD-PhD program at Thomas Jefferson University. He has been awarded a PhRMA Foundation Pre-Doctoral Fellowship to assist his training in the Waldman laboratory. His research focuses on gut-neural endocrine regulation of appetite and pharmacologic interventions for the prevention and treatment of obesity. He has published several articles on anti-obesity pharmacotherapy and has been the recipient of several awards based on his research. He is currently in his final year of training and will be pursuing a clinical residency in the field of Internal Medicine.

Scott A. Waldman received his PhD in Anatomy from Thomas Jefferson University and his medical school, internal medicine and clinical pharmacology training from Stanford University. He returned to Thomas Jefferson University in 1990, where he is the Vice President for Clinical and Translational Research, Associate Dean for Clinical and Translational Science, Chair of the Department of Pharmacology & Experimental Therapeutics and the Samuel MV Hamilton Professor of the Department of Medicine. Dr. Waldman's research focuses on the intersection of molecular mechanisms underlying obesity, metabolic diseases and gastrointestinal malignancies.

Table 1

Current medications used for obesity

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 drug (05/1959)
	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	FDA-approved drug (10/1960)
	Diethylpropion	FDA-approved drug (08/1959)
	Phendimetrazine	FDA-approved drug (09/1982)
	Dexfenfluramine	FDA-approved drug (06/1973) for fenfluramine (04/1996), but withdrawn (09/1997) due to cardiovascular effects
	Fenfluramine	
Inhibits the neuronal uptake of dopamine, norepinephrine, and serotonin.	Bupropion	Off-label usage
Serotonin, dopamine and norepinephrine reuptake inhibitor (SNRI) that potentiates the neurotransmitter activity in the central nervous system (CNS).	Desvenlafaxine	Off-label usage
	Sibutramine	FDA-approved drug (11/1997), but withdrawn (10/2010) due to cardiovascular effects
Selective cannabinoid-1(CB-1) receptor antagonist.	Rimonabant	EMA-approved drug (06/2006), but withdrawn (10/2008) due to possible suicide and psychiatric effects
The exact mechanism of action is unknown.	Topiramate	Off-label usage
Reversible inhibitor of intestinal lipases.	Orlistat	FDA-approved drug (04/1999)
Glucagon-like peptide-1(GLP-1) receptor agonist.	Exenatide	Off-label usage
	Liraglutide	Off-label usage
Inhibitor of dipeptidylpeptidase-4.	Alogliptin	Off-label usage
	Saxagliptin	Off-label usage
	Sitagliptin	Off-label usage
	Vildagliptin	Off-label usage
Amylin analog.	Pramlintide	Off-label usage

Table 2

Anti-obesity drugs in development

Target	Drug	Company	Mechanism of action	Status
Central neuropeptide signaling				
Melanin-concentrating hormone	ALB-127158	AMRI	MCH1 antagonist	Phase I completed
	BMS-830216	Bristol-Myers Squibb	MCH receptor antagonist	Phase II recruiting
Melanocortin receptor	MK-0493	Merck	Selective MC4R agonist, increasing MC3/4R signaling	Phase II completed
	TM30339	7TMPharma	Selective Y4-receptor agonist	Phase II completed
	TTP435	TransTech Pharma	AgRP inhibitor, increasing MC3/4R signaling	Phase II completed
NPY	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/ Natestch	Y4R agonist in DVC, Y2R agonist in arcuate nucleus	Phase I/II
	PYY ₃₋₃₆ /SNAC	Emisphere	Y4R agonist in DVC, Y2R agonist in arcuate nucleus	Phase I/II
	Velneperit(S-2367)	Shionogi USA	Y5 receptor antagonist, NPY blocker	Phase II completed
Monoamine neurotransmission				
Dopamine / norepinephrine /serotonin	Contrave (bupropion / naltrexone)	Orexigen	Norepinephrine/dopamine reuptake inhibitor	Safety study requested in Feb 2011 due to cardiovascular risk
	GSK598809	GlaxoSmithKline	Dopamine (D3) antagonist	Phase I completed
	Empatic™ (zonisamide SR/bupropion SR)	Orexigen	Norepinephrine/dopamine reuptake inhibitor GABA receptor activator	Phase II completed
	Lorcaserin HCl	Arena / Eisai	Selective 5HT _{2C} receptor agonist	Rejected in Oct 2010 due to marginal effects
	Qnexa® (phentermine/ topiramate)	Vivus	Norepinephrine releasing agent GABA receptor activator	Safety study requested in Jan 2011 due to possible birth defects
	Tesofensine (NS2330)	NeuroSearch	Serotonin / norepinephrine/ dopamine reuptake inhibitor	Phase II
Histamine	A-331440	Abbott Laboratories	Non-imidazole histamine H ₃ receptor antagonist	Pre-clinical
	HPP404	TransTech Pharma	Selective H3 receptor antagonist	Phase IIa recruiting
	SCH-497079	Schering-Plough	Histamine receptor antagonist	Phase II completed
Intestinal peptide hormone signaling				
CCK	GI 181771X	GlaxoSmithKline	CCK-A agonist, mimicking the effect of CCK	Terminated

Target	Drug	Company	Mechanism of action	Status
Ghrelin	AEZS-123	AEterna Zentaris	Ghrelin receptor antagonist	Pre-clinical
	CYT009-GhrQb	Cytos	First-generation ghrelin vaccine, bind and inhibit ghrelin	Terminated
	Spiegelmer®(NOX-B11)	Pfizer/ Noxxon	Bind and inhibit ghrelin	Phase I completed
GLP-1	NN9924	Novo Nordisk	GLP1R agonist, GLP-1 mimicking	Phase I completed
	Byetta® (exenatide)	Amylin	GLP1R agonist, GLP-1 mimicking	Phase III completed
OXM	Qxyntomodulin (OXY-RPEG)	Prolor	GLP1R agonist, OXM mimicking	Phase I recruiting
	TKS1225	Thiakis/Wyeth/Pfizer	GLP1R agonist, OXM mimicking	Phase I
Pancreatic hormone signaling				
PP	PP1420	Wellcome Trust	Pancreatic polypeptide analog	Phase I completed
Amylin	Davalintide(AC2307)	Amylin	Amylin mimicking	Phase II
Adipose tissue hormone signaling				
Leptin	Metre leptin	Amylin/Takeda	Leptin receptor agonist	Phase III recruiting
Inhibition of lipase				
Pancreatic lipase	Cetilistat(ATL-962)	Alizyme/Takeda/ Norgine	Pancreatic lipase inhibitor, inhibiting intestinal lipid absorption	Phase II completed
Other				
MetAP2	Fumagillin	Zafgen	Methionine aminopeptidase 2 inhibitor	Pre-clinical
	ZGN-433	Zafgen	Methionine aminopeptidase 2 inhibitor	Phase I completed
DGAT1	AZD7687	AstraZeneca	Diglyceride acyltransferase inhibitor, inhibiting triglyceride synthesis	Phase I completed
11 β-HSDI	AZD4017	AstraZeneca	11 β -HSDI inhibitor	Phase IIa recruiting
	AZD8329	AstraZeneca	11 β -HSDI inhibitor	Phase I completed
	INCB13739	Incyte	11 β -HSDI inhibitor	Phase I completed