New Drug Targets for the Treatment of Obesity

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There is a huge void in the current pharmacological treatment options for obesity. This gap is surprising given the high prevalence and associated costs of obesity. Many factors have prevented active drug development, including the poor safety and efficacy of earlier antiobesity drugs. However, there are now several compelling targets on the horizon. The new generation of antiobesity drugs offers hope for the management of obesity, but no single agent is likely to be a panacea. Rather, obesity will need to be managed like many other chronic diseases, with combination therapies and long-term treatment in order to achieve sustained success. New targets have arisen as more research has been performed to understand the complex circuitry that controls energy homeostasis. The goal of this review is to discuss the latest pharmacological agents and strategies that are under development and that may eventually be used for the treatment of obesity.

Obesity affects approximately one-third of the US population, and its prevalence has doubled over the past three decades. The prevalence of obesity (defined as a body mass index (BMI) $\geq 30\,kg/m^2$) increased from 15% in 1980 to 33.8% in 2008,[1] while the prevalence of overweight (defined as a BMI $\geq 25\,kg/m^2$) among adults in the United States reached 68%. The International Obesity Task Force estimates that, worldwide, at least 1.1 billion adults are overweight, including 312 million who are obese.

Obesity is associated with several comorbidities, including hypertension, type 2 diabetes (DM), osteoarthritis, dyslipidemia, obstructive sleep apnea, and some cancers.[2] Many of these diseases can be prevented or ameliorated with a reduction in body weight. In fact, obesity has been identified as the second most common factor contributing to preventable death (second only to tobacco).[3] In addition, the economic cost of obesity-associated diseases is approaching $100 billion per year in the United States.[4]

The medical goal for weight loss is no longer considered achievement of an ideal body weight. Rather, achieving a 10% reduction in total body weight is a more reasonable expectation given that this amount of weight loss can reduce the health risks associated with obesity.[5] In the Swedish Obese Subjects study, the incidence of new cases of DM was reduced to zero over a period of 2 years in patients who lost >12% of their body weight and then maintained the lower weight; in contrast, the incidence of new cases of DM was 8.5% in those who did not lose any weight.[6] In the Diabetes Prevention Program, patients with a baseline BMI $>24\,kg/m^2$ who had a modest weight loss of 5.6 kg (7%) had a 58% reduction in the risk of developing diabetes.[7]

Current strategies for the management of obesity include dietary and exercise-related changes and behavior modification (BMOD). Diet and exercise strategies alone, although successful in the short term, are difficult to maintain in the long term for the majority of patients. Because of weight regain, such attempts at weight loss have not been shown to significantly reduce the obesity-related disease burden.[8] Research has shown that only 20% of overweight individuals are successful at long-term weight loss, defined as losing $\geq 10\%$ of initial body weight and maintaining the loss for at least 1 year. Given the limitations in achieving weight control with diet and exercise alone, medications and alternative treatment options have been sought.

The criteria set forth by the US Food and Drug Administration (FDA) for a drug to be approved for treatment of obesity require that it induce statistically significant placebo-adjusted weight loss of >5% at 1 year or that >35% of patients should achieve >5% weight loss (which must be at least twice that induced by placebo). The FDA also requires that the medication show evidence of improvement in metabolic biomarkers, including blood pressure, lipids, and glycemia. Several past attempts at developing an effective weight-loss drug have been unsuccessful because they failed to meet the safety and efficacy profiles.

Currently, there are only two FDA-approved drugs available for the treatment of obesity: phentermine and orlistat (**Table 1**). Phentermine, approved in 1959, is the most

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commonly prescribed antiobesity agent in the United States. It is a sympathomimetic amine that suppresses appetite. The approved duration of treatment is only 3 months because of concerns over longer-term safety.[9] Data show that, when used as monotherapy, phentermine can induce an 8–10% weight loss; however, the average weight loss usually reaches a plateau at 3–6 months. Concerns about side effects such as elevation in blood pressure and heart rate limit its use in many patients. Orlistat, which was approved in 1999, is an oral lipase inhibitor that acts by reducing the absorption of dietary fat. However, only 15–30% of patients achieve >5% weight loss after 1 year of therapy. In addition, orlistat can have significant gastrointestinal side effects, especially if dietary fat intake is much more than 30% of total daily caloric intake; this limits its tolerability in many patients.

Unfortunately, the antiobesity medications in the clinicians' armamentarium are few in number. This is in part because one of the biggest challenges in developing antiobesity drugs is the poor safety profile. Historically, the limitations have been due to a variety of concerns (Table 2). These include valvulopathy associated with fenfluramine and dexfenfluramine, the abuse potential and psychiatric side effects associated with

rimonabant, and, most recently, cardiac adverse events associated with sibutramine.[10]

New targets have been identified as more research has been performed to understand the complex circuitry controlling energy homeostasis. The goal of this review is to discuss the latest pharmacological agents that are under development and that may eventually be used for the treatment of obesity (Table 3).

COMBINATION THERAPY

New drug therapy has begun to focus on combination treatments. The rationale behind a combination treatment approach is that food intake is modulated by various mechanisms that might allow a homeostatic response to counterregulate the effect of modulating any single mechanism. Therefore, by using multiple agents to target more than one of these mechanisms, more favorable weight-loss outcomes may be achieved than with any

Table 1 History of antiobesity medications

Drug	FDA approval date	FDA withdrawal date
Phentermine	5/1959	
Fenfluramine	6/1973	9/1997
Dexfenfluramine	4/1996	9/1997
Orlistat	4/1999	
Sibutramine	11/1997	10/2010
Rimonabant	6/2006[a]	10/2008
Diethylpropion	8/1959	
Benzphetamine	10/1960	
Phendimetrazine	9/1982	

FDA, US Food and Drug Administration. [a]The drug (Rimonabant) was not approved by the FDA in the United States. It was an approved drug on the market in Europe, but has since been recalled.

Table 3 Promising drugs for the treatment of obesity

Phase III drugs	
Empatic (zonisamide + bupropion)	Antiepileptic dopamine and noradrenaline reuptake inhibitor
Pramlintide/metreleptin	Leptin analog + amylin analog
Cetilistat	Pancreatic lipase inhibitor
Phase II drugs	
Liraglutide	Long-acting GLP-1 analog
Tesofensine	Triple monoamine reuptake inhibitor
Velneperit	Neuropeptide Y5 receptor antagonist
Obinepitide	PYY3-36 and pancreatic polypeptide analog
Phase I drugs	
TPN435	AgRP (agouti-related protein) inhibitor
ZGN-433	MetAP2 (methionine aminopeptidase 2) inhibitor
PP1420	Pancreatic polypeptide analog
GSK 598809	D3 (dopamine) antagonist
AZD 7687	DGAT1 (diglyceride acyltransferase) inhibitor

GLP-1, glucagon-like peptide-1.

Table 2 Drug treatments for obesity recently reviewed, rejected, or withdrawn by the FDA

Drug	Mechanism of action	Reason for lack of approval/withdrawal
Sibutramine	Noradrenaline and serotonin reuptake inhibitor	Withdrawn from market due to concern over increased risk of heart attack and stroke in high-risk cardiac patients
Rimonabant	CB1 receptor antagonist	Not approved in United States due to concern over psychiatric side effects
		Withdrawn from European market in 2009 due to increased risk of suicide
Lorcaserin	Selective 5HT-2C receptor antagonist	Not approved due to concerns over carcinogenicity observed in rats
Contrave (bupropion + naltrexone)	Dopamine and noradrenaline reuptake inhibitor, μ-opioid antagonist	FDA requested data on long-term cardiovascular risks
Qnexa (phentermine + topiramate)	Sympathomimetic agent, weak carbonic anhydrase inhibitor; exact mechanism for weight loss unknown	FDA requested data on teratogenic potential

FDA, US Food and Drug Administration.

single agent alone. It has also been proposed that targeting more than one mechanism may actually provide a better safety profile, given that many of the agents to be discussed are already established drugs that are tolerated and approved. Finally, the safety ratio may be improved by the use of lower doses.

Qnexa

Qnexa (Vivus Pharmaceuticals, Mountain View, CA) is a combination therapy consisting of lower doses of topiramate and phentermine than are usually prescribed. Topiramate has been approved for migraine prophylaxis and the treatment of seizure disorders. Phentermine, an amphetamine derivative, has been on the market for more than 30 years for short-term treatment of obesity.

Initial studies of topiramate, when used for other indications, demonstrated an unexpected weight-loss benefit.[11] Two multicenter, placebo-controlled trials demonstrated significant dose-dependent weight loss in obese subjects given topiramate at doses of 96–256 mg. The safety population consisted of 1,282 subjects, and the modified intention-to-treat (MITT) efficacy population was 854 subjects. At 60 weeks, subjects in the placebo group had lost 1.7% of their baseline body weight, while subjects in the topiramate 96, 192, and 256 mg/day treatment groups lost 7.0, 9.1, and 9.7% of baseline body weight, respectively. Unfortunately, adverse events at the higher doses were limiting.[12]

The mechanism through which topiramate suppresses appetite is not entirely understood. Topiramate is a weak carbonic anhydrase inhibitor, with selectivity for carbonic anhydrase isoforms II and IV; it also modulates the γ-aminobutyric acid-A receptors and exhibits state-dependent blockage of voltage-dependent Na or Ca channels (all of which may contribute to its antiepileptic properties). The modulation of γ-aminobutyric acid may have a role in the reduction of food intake, but the mechanism for this is not entirely clear.[13]

The rationale for combining topiramate with phentermine is to minimize the required dosage of each of the medications, thereby helping to reduce side effects while simultaneously opening up more than one pathway to satiety in the hope of achieving greater efficacy.

Vivus has completed three phase III studies of Qnexa. EQUATE, a 28-week confirmatory factorial trial with seven arms, tested two fixed-dose combinations—mid-dose Qnexa (7.5 mg phentermine, 46 mg topiramate) and full-dose Qnexa (15 mg phentermine, 92 mg topiramate)—as well as the individual drug components of these fixed-dose combinations. The study involved 756 subjects with BMI values of 30–45 kg/m^2. The coprimary end points of the trial were mean weight loss and the percentage of subjects achieving weight loss ≥5% of their body weight. Vivus reported that the trial met its primary end point by demonstrating statistically significant weight loss with both mid-dose Qnexa and full-dose Qnexa, relative to placebo.[14] Patients treated with full-dose Qnexa achieved an average weight loss of 9.2%, as compared to the loss of 1.7% ($P < 0.0001$) by those in the placebo group. The mid-dose Qnexa group's average weight loss (8.5%) was comparable to that of

full-dose patients. Both doses were well tolerated, the most common side effects being paresthesia (mid-dose: 15%; full-dose: 20%; placebo: 3%), dry mouth (mid-dose 12%; full dose 18%; placebo: 0%), constipation (mid-dose: 6%; full-dose: 11%; placebo: 6%), and altered taste (mid-dose: 8%; full-dose: 15%; placebo: 0%). In January 2009, after a follow-up analysis for the EQUATE trial, it was reported that patients without diabetes who received treatment with Qnexa showed a statistically significant lowering of blood sugar relative to patients on placebo, as measured by hemoglobin A_{1c} (HbA_{1c}).

A second phase III trial, EQUIP, enrolled 1,267 morbidly obese patients (mean BMI 42.1 kg/m^2) over a period of 56 weeks. After 4 weeks of dose titration, the patients were given the low-dose combination (3.75 mg phentermine, 23 mg topiramate), the full-dose combination (15 mg phentermine, 92 mg topiramate), or placebo.[15] In an intention-to-treat population using last-observation-carried-forward (ITT-LOCF) analysis, the mean weight loss in the placebo group was 1.6%, as compared to 5.1% in the low-dose group and 11% in the full-dose group. The mean percentage of subjects achieving ≥5% weight loss was 17% in the placebo group, 45% in the low-dose group, and 67% in the full-dose group. In the completer analysis, the mean weight loss was 2.5, 7, and 14% for the placebo, low-dose, and full-dose groups, respectively. The most common side effects were paresthesia (1.9, 4.2, and 18.8%, respectively), dry mouth (3.7, 6.7, and 17%), constipation (6.8, 7.9, and 14.1%), and dizziness (4.1, 2.9, and 5.7%). The completion rate for subjects taking either dose of Qnexa was 69% and was significantly higher than for placebo.

In the third phase III trial, CONQUER, 2,487 obese subjects (mean BMI 36.3 kg/m^2) were randomly assigned to receive placebo, the mid-dose combination (phentermine 7.5 mg, topiramate controlled-release 46 mg), or the high-dose combination (phentermine 15 mg, topiramate controlled-release 92 mg) for 56 weeks.[16] The coprimary end points of the study were mean percentage weight loss and the percentage of subjects achieving weight loss ≥5%. At week 56, changes in body weight were −1.4 kg (−1.2%), −8.1 kg (−7.8%), and −10.2 kg (−9.8%) for patients assigned to placebo, mid- and high-dose groups. Per the completer analysis, the mean weight loss was −1.8 kg (−1.6%), −9.9 kg (−9.6%) and −12.9 kg (−12.4%) in the placebo, mid-dose and full-dose groups, respectively.[17] Dropout rates during the study were 43% in the placebo arm, 31% in the mid-dose arm, and 36% in the full-dose arm.

The weight loss seen with Qnexa was associated with a reduction in blood pressure across all doses. However, the highest dose was associated with an increase in heart rate of 1.5 bpm. No elevation in heart rate was noted in the mid-dose or low-dose groups. Other outcome measures that indicated beneficial effects included an amelioration of obstructive sleep apnea as measured by the apnea–hypoxia index. In a subset analysis of high-risk patients treated with high-dose Qnexa (high-risk being defined as being in the upper 25th percentile of a specific comorbidity), there were significant improvements in a number of cardiovascular risk factors. In the treatment groups, there was a reduction of 20 mm Hg in systolic blood pressure (vs. 14 mm Hg in the placebo group) and a reduction of 98 mg/dl in triglycerides (from 268 mg/dl at

baseline) as compared with a decrease of 42 mg/dl (from 262 mg/dl at baseline) in the placebo group. In addition, the treatment-group patients showed a reduction in HbA_{1c} of 0.6% (from 7.3% at baseline) as compared with 0.1% (from 7.4% at baseline) in the placebo group.

In a pooled analysis of data from EQUIP and CONQUER, adiposity and cardiometabolic risk markers were evaluated. There was a mean reduction in total percentage adiposity in the treatment groups that was significantly greater than that in the placebo group. In addition, there were reductions in waist circumference, lipid levels, and glycemic parameters[18] and a reduction in mean plasma alanine transaminase concentration, which has been used as a surrogate marker for nonalcoholic fatty liver disease, a common complication of obesity.[19]

The most significant side effects of Qnexa treatment included dry mouth, paresthesia, constipation, altered taste, and insomnia. The rate of discontinuation due to cognitive dysfunction (including inattention, amnesia, and memory impairment) was 0.9%, which is favorable compared with average discontinuation rates during topiramate monotherapy (3–4%).

On 15 July 2010, the Endocrinologic and Metabolic Advisory Committee evaluated Qnexa and recommended against approval by the FDA. The members focused on five key safety issues: psychiatric adverse events, cognitive adverse events, metabolic acidosis, teratogenicity, and cardiovascular adverse events. They cited as additional issues the lack of cardiovascular outcomes data and the relatively short-term (12 months) safety database available for a drug that could potentially be used to treat high-cardiovascular-risk patients and young women for several years. Of note, no birth defects, including cleft palate, were noted in the phase III trials despite 15 pregnancies. Also, when topiramate is prescribed for seizure disorders, it is often continued throughout pregnancy; this would not be the case if it were used as an antiobesity agent. In response to FDA concerns, Vivus proposed a large postmarketing cardiovascular risk trial.

In September 2010, Vivus announced top-line results from its 2-year, placebo-controlled, prospective SEQUEL (OB-305) study of Qnexa, a 675-patient 52-week extension study of the phase III CONQUER study.[20] The efficacy data were robust, and the safety data were consistent with those reported in previous phase III studies. The most common adverse events were constipation, tingling, dry mouth, altered taste, and insomnia. Patients receiving the high dose of Qnexa achieved a 2-year average weight loss of 10.5% of their body weight, and patients receiving the mid-dose achieved a 2-year weight loss of 9.3% as compared to the placebo group, which had an average weight loss of 1.8%. In both groups, weight loss was associated with statistically significant improvements with respect to comorbidities such as hypertension, dyslipidemia, and diabetes.

Categorical weight-loss responder rates in the ITT-LOCF population in patients achieving weight loss of ≥10% were 54% for patients in the high-dose Qnexa group, 50% for patients in the mid-dose group, and 12% for patients in the placebo group ($P < 0.0001$). Discontinuation rates in the SEQUEL study were 4.1, 3.9, and 2.6% in the high-dose, mid-dose, and placebo groups,

respectively. Neither suicide attempts nor suicidal behavior were observed in any of the patients in the study, and PHQ-9 clinical depression measurements showed an amelioration of depression relative to baseline in patients receiving Qnexa. There were no reports of teratogenic effects associated with the use of Qnexa in the SEQUEL study, consistent with the observations from the other phase III studies.

In October 2010, the FDA did not approve Qnexa in its current form and requested more evidence that the elevated heart rate associated with its use does not increase cardiovascular risk. In addition, the agency had concerns regarding the teratogenic potential of the drug. In January 2011, Vivus announced that the FDA had requested additional information regarding teratogenicity and that the company will continue to work with the FDA in an effort to secure approval for the drug.[21]

Contrave

A dual antiobesity agent, Contrave is a combination of the known antidepressant bupropion and the opioid antagonist naltrexone.

Bupropion is an inhibitor of dopamine and noradrenaline reuptake. It was originally approved both for treating depression and for inducing smoking cessation. During initial clinical trials, it was noted that it suppressed appetite and food cravings.[22] In clinical studies of bupropion as monotherapy, the average weight loss was 2.8 kg at 24–52 weeks[23]; as a single agent, therefore, bupropion does not meet FDA criteria for an antiobesity drug.

Bupropion also stimulates pro-opiomelanocortin (POMC) firing in the arcuate nucleus of the hypothalamus. POMC firing subsequently releases α-melanocyte stimulating hormone, which mediates the anorectic effect of POMC.[24] However, POMC neuronal stimulation results in a negative-feedback loop through release of B-endorphin, activating opioid receptors on POMC and controlling further POMC firing.[25] It has been hypothesized that the early plateauing of the effects of bupropion, making its efficacy poor as a single agent, may be due partly to this negative feedback. The addition of naltrexone, a μ-opiate antagonist, was considered as a means to achieve greater weight loss and counter the negative feedback associated with bupropion.

Initial studies demonstrated that the combination of these two medications was effective in producing weight loss in obese adults. In 2009, Greenway *et al*. conducted a double-blind placebo-controlled study, enrolling 419 obese subjects (BMI 30–40 kg/m^2) over a period of 24 weeks. The subjects were randomized to receive one of the following: placebo, naltrexone 48 mg alone, bupropion slow-release (SR) 400 mg, or combinations of bupropion 400 mg with varying doses of naltrexone (16 mg, 32 mg, and 48 mg). At 24 weeks, the average weight loss in each of the groups was as follows: naltrexone alone, 1.1 kg; placebo, 0.9 kg; bupropion alone, 2.6 kg; 400 mg bupropion/16 mg naltrexone, 5.1 kg; 400 mg bupropion/32 mg naltrexone, 5.1 kg, and 400 mg bupropion/48 mg naltrexone, 4 kg. At a 48-week extension time point, the weight loss increased to 7.4 kg, 8.2 kg, and 10 kg, respectively, in the three combination treatment groups.[26]

These data endorse the hypothesis that two drugs working synergistically and in combination provide greater weight loss than either of them singly.

Orexigen Pharmaceuticals conducted four phase III clinical trials, of which COR-I was the first. It was a 56-week placebo-controlled, double-blind, randomized trial in patients with BMI 30–45 kg/m^2 (uncomplicated obesity) and 27–45 kg/m^2 (with controlled hypertension or dyslipidemia, or both).[27] The subjects (N =1,742) were randomized in a 1:1:1 ratio to one of the following treatment arms: NB32 (32 mg naltrexone SR + 360 mg bupropion SR), NB16 (16 mg naltrexone SR + 360 mg bupropion SR), or placebo. The dose was escalated in a linear fashion over 3 weeks, with the maintenance dose being achieved by 4 weeks. A modified ITT-LOCF analysis showed that the average weight loss was 5% in the NB16 group, 6.1% in the NB32 group, and 1.3% in the placebo group. Results from COR-I showed that treatment with Contrave resulted in significant reductions (as compared to placebo treatment) in waist circumference, insulin resistance, high-density lipoprotein cholesterol, triglycerides, and high-sensitivity C-reactive protein, which are well-known and accepted measures of cardiometabolic risk. Mean systolic blood pressure decreased by 1.6 mm Hg from baseline to end point in patients receiving NB32 vs. 2.8 mm Hg in patients on placebo. Patients taking Contrave also showed significant improvements in patient-reported control of eating, including reduction in food cravings as well as reduced difficulty in resisting food cravings. NB treatment was generally well tolerated, the most common adverse events being nausea, constipation, vomiting, and dry mouth. Adverse events in the Contrave groups were generally transient and mild to moderate in intensity, and for most patients did not result in discontinuation of the study.

In a second phase III randomized controlled trial, subjects were assigned to a 56-week course of either placebo + BMOD or NB32 + BMOD (naltrexone 32 mg SR + bupropion 360 mg SR).[28] The primary end points were the percentage change in body weight from baseline at week 56 and the percentages of patients achieving ≥5% total loss in body weight. A modified ITT-LOCF analysis showed that the BMOD group lost 9.3% of their initial body weight vs. 5.1% in the placebo + BMOD group. The percentages of subjects who lost ≥5% of their baseline body weight were 66.4% in the BMOD group and 42.5% in the placebo + BMOD group ($P < 0.001$). Secondary analyses showed that the percentages of subjects who lost ≥10% of their baseline body weight were 41.5% in the BMOD group vs. 20.2% in the placebo + BMOD group ($P < 0.001$). Also, 29.1% of the NB32 group lost ≥15% of their body weight vs. 10.9% of the placebo group ($P < 0.001$). The major treatment-emergent adverse events were nausea, constipation, and dizziness. The overall rate of discontinuation due to adverse events was 25.9% in patients receiving NB32 vs. 13% in those receiving placebo. Nausea was the most frequent adverse event leading to discontinuation of the study drug (4.6% in the BMOD group vs. 0% of placebo).

In December 2010, the FDA's Endocrinologic and Metabolic Drugs Advisory Committee voted 13 to 7 to support approval of Contrave on the grounds that the potential benefits of the drug outweighed its potential risks when used long term in a population of overweight and obese individuals. However in their complete response letter issued January 31, 2011, the FDA asked for a preapproval cardiovascular outcome study to demonstrate that the risk of major adverse cardiovascular events in subjects treated with naltrexone/bupropion does not adversely affect the drug's benefit-risk profile.

Therefore, despite the fact that the FDA Metabolic and Endocrine Advisory Committee voted in favor of granting approval to Contrave, and the long history of safe use of its components, the FDA officially chose a more conservative approach that could potentially prevent this compound from entering the marketplace.

Empatic

Empatic is the combination drug of zonisamide and bupropion. Zonisamide is an antiepileptic drug approved for the treatment of partial seizures. Clinically, it has been shown to induce weight loss as a side effect.[29] The precise mechanism is unknown; however, a possible mechanism is sodium channel modulation and enhancement of dopamine and serotonin neurotransmission, potentially resulting in weight loss.

Bupropion, approved for the treatment of depression and later for smoking cessation, has also been linked to weight loss.[30] With this drug, the weight loss is thought to be caused by a drug-induced increase in the level of dopamine, which could lead to a reduction in appetite. The addition of bupropion to zonisamide as an antiobesity combination therapy was designed to ameliorate the side effects and improve the efficacy relative to either of these drugs given as monotherapy. More specifically, it was thought that bupropion might offset the depressive and sedative properties associated with zonisamide, while the latter might reduce the likelihood of bupropion-induced seizures.[31]

Initial studies evaluating the combination of bupropion + zonisamide demonstrated improved weight loss as compared to either medication administered singly. In a small pilot study, 18 obese women were given either zonisamide immediate-release (IR) or bupropion as monotherapy, or the combination of the two, for 12 weeks; there was no placebo group.[31] Zonisamide was initially given at a dose of 100 mg and the dose was titrated to 400 mg at 4 weeks. Bupropion was administered at 100 mg IR, increasing to 200 mg after 2 weeks. ITT-LOCF analysis showed that the zonisamide monotherapy group had an average weight loss of 2.9 kg (3.1%) at 12 weeks as compared to 7.2 kg (7.5%) achieved in the combination therapy group. Zonisamide monotherapy was noted to be poorly tolerated, causing fatigue, drowsiness, and speech/language difficulties, and there was a 44% dropout rate. The combination therapy was better tolerated, the dropout rate being only 22%.

In September 2009, Orexigen released data from a 24-week phase IIb double-blind, placebo-controlled trial of Empatic in 729 obese patients (BMI range 27–45 kg/m^2).[32] The patients were randomized to one of six arms: two Empatic groups (bupropion IR 360 mg + zonisamide SR 120 mg and bupropion IR 360 mg + zonisamide SR 360 mg), three single-treatment groups (bupropion IR 360 mg, zonisamide SR 360 mg, and zonisamide SR 120 mg), or placebo. ITT-LOCF analysis showed that the primary end point

was met, in that Empatic demonstrated greater weight loss vs. its individual components as well as vs. placebo. Specifically, the combination therapy containing 120 mg of zonisamide resulted in a weight loss of 6.1%, while the one containing a higher dose of zonisamide (360 mg) resulted in a weight loss of 7.5%. Both of these combinations produced weight-loss effects that were significantly superior to that of placebo (1.4% weight loss) and also superior to the zonisamide doses given as monotherapy. The zonisamide 120 mg and 360 mg monotherapy arms resulted in weight losses of 3.2 and 5.3%, respectively. Bupropion 360 mg given as monotherapy induced a weight loss of 2.3%. Overall, 60.4% of the subjects in the high-dose Empatic group and 46.9% of those in the low-dose Empatic group showed a weight loss >5%. In the high- and low-dose groups, 32.3 and 24.7% of the subjects, respectively, had a weight loss >10%.

At 24 weeks, there was no evidence of a plateau in weight loss, thereby suggesting that even greater efficacy could be seen in 1-year trials. The most common side effects were nausea, headache, and insomnia. The discontinuation rates were 34% for the high-dose Empatic group vs. 29% for the placebo group. No patient experienced serious adverse events due to Empatic. The occurrence of depression, impaired cognitive function, anxiety, and suicidality were not significantly different between the placebo and Empatic groups.

Plans for phase III Empatic trials have not yet been announced.

Pramlintide/metreleptin

Leptin is a hormone produced by adipocytes, and early studies linked leptin deficiency in mice to massive obesity. Initially there was hope that leptin would be a successful treatment option to combat obesity. It was assumed that obese humans must be leptin-deficient; however, research has shown the opposite. Many clinical trials failed to demonstrate any benefit of treatment with recombinant human leptin. In fact, leptin levels have been shown to be up to 10-fold higher in individuals with BMI >30 kg/m^2. It is also possible that the persistence of obesity in the presence of leptin may indicate that leptin is failing to exert its weight-reducing action—therefore humans with obesity must be "leptin-resistant."[33] Given the lack of clinical efficacy of leptin administered alone, mechanisms to overcome leptin resistance have been sought.

Amylin is a peptide hormone with both glucose-regulatory and anorexigenic actions.[34] Amylin is stored in the pancreatic A-cell secretory vesicles and secreted in response to food intake. Plasma amylin concentrations rise rapidly after meals in proportion to meal size and peak 30 min after a meal. Amylin acts in the hindbrain area postrema and central nucleus of the amygdala to reduce food intake, by acting as a satiety signal.[35]

Pramlintide, a synthetic form of amylin, when administered peripherally to rats with diet-induced obesity, produces a sustained reduction in food intake and body weight.[36] Clinical studies have shown that pramlintide, a medication currently approved in the United States for the treatment of type 1 or 2 diabetes, leads to reduction in food intake and body weight in obese humans, in both those with diabetes and those without.[37]

Leptin is a long-term adiposity signal, whereas amylin, which is secreted in response to meals, is a short-term satiety signal. The potential interaction of a long-term signal with a short-term one became an area of interest because it was thought that the effects might be additive or synergistic. The results of mechanistic studies in rats pretreated with amylin suggested that leptin signaling within the hypothalamus and caudal hindbrain may modulate the observed weight-loss synergy, such that the presence of amylin may "prime" the hypothalamus to respond better to leptin.[38]

In a phase IIa, 24-week, proof-of-concept study conducted by Amylin Pharmaceuticals, 177 overweight or obese subjects were randomized to receive pramlintide, metreleptin, or a combination of the two. After a 4-week lead-in period with pramlintide (180 μg b.i.d. for 2 weeks, 360 μg b.i.d. thereafter) and dieting, the subjects who achieved 2–8% weight loss were randomized to 20 weeks of treatment with metreleptin (5 mg intradermal), pramlintide (360 μg b.i.d.), or the combination of the two (metreleptin 5 mg b.i.d. + pramlintide 360 μg b.i.d.). Combination treatment with pramlintide + metreleptin led to significantly greater weight loss (12.7%) than either of the constituents given singly (8.4% with pramlintide and 8.2% with metreleptin). The most common adverse events were injection-site events and nausea, which were mostly mild to moderate and decreased over time.[39]

On the basis of these significant results, a 28-week phase IIb clinical trial of pramlintide + metreleptin was completed in late 2009, followed by an extension study up to 52 weeks.[40] The 28-week, double-blind, placebo-controlled study enrolled 608 obese or overweight subjects (BMI 27–45 kg/m^2). After a 1-week placebo lead-in period, the subjects were randomized to twice-daily therapy with one of eight regimens: (i) placebo + placebo, (ii) pramlintide 360 μg + placebo, (iii) metreleptin 5 mg + placebo, (iv) pramlintide 180 μg + metreleptin 2.5 mg, (v) pramlintide 180 μg + metreleptin 5 μg, (vi) pramlintide 360 μg + metreleptin 1.25 mg, (vii) pramlintide 360 μg + metreleptin 2.5 mg, or (viii) pramlintide 360 μg + metreleptin 5 mg. The magnitude of the weight loss was found to be dependent on dose and baseline BMI. At 28 weeks, evaluable patients with a baseline BMI <35 kg/m^2 and treated with the highest pramlintide + metreleptin doses had an average weight loss of 11% ($P < 0.01$), which was greater than the weight loss in the placebo group (1.8%) and in the groups that received either of the agents singly (~5%).

Amylin announced further results of the 52-week extension in February 2010. The company reported that patients treated for 52 weeks demonstrated sustained weight loss, whereas those on placebo regained almost all the weight they had lost.[41] At the time of writing this paper, Takeda and Amylin have initiated phase IIb trials.

MONOTHERAPY IN PHASE II/III TRIALS
Lorcaserin

Lorcaserin is a 5-HT receptor agonist that mediates serotonin in the central nervous system. The distinguishing characteristic of lorcaserin is that it exhibits selectivity within the 5HT receptor classes; therefore, it has a more favorable side-effect profile than previous 5HT receptor-agonist targets.

Fenfluramine, a previously marketed nonselective 5HT agonist, was highly successful in inducing weight loss. Fenfluramine targeted 5HT-2C in addition to 5HT-2B and 5HT-2A. It has been shown that 5HT-2A receptors are hallucinogenic,[42] whereas 5HT-2B receptor activation is associated with the development of valvulopathy[43] and primary pulmonary hypertension.[44] Therefore the risks associated with the use of fenfluramine, namely valvulopathy and primary pulmonary hypertension, are probably due to the affinity of the drug for these peripheral targets.

Lorcaserin has a high affinity for the 5HT-2C subtype, with only modest binding to 5HT-2A and 5HT-2B; it has therefore become a target of interest.[45] In an initial phase II, double-blind, placebo-controlled trial, lorcaserin was administered to 469 obese subjects over a period of 12 weeks without diet or lifestyle modification.[46] ITT-LOCF analysis showed that subjects who received 10 or 15 mg daily or 10 mg b.i.d. doses had progressive, placebo-adjusted weight losses of 1.5, 2.0, and 2.9 kg, respectively. Echocardiograms performed during the trial did not show any evidence of valvulopathy or pulmonary hypertension.

Two phase III trials have been completed. The first, BLOOM, was a double-blind, placebo-controlled study of 3,182 obese or overweight adults. They received lorcaserin 10 mg b.i.d. or placebo for 52 weeks, in conjunction with a prescribed diet and exercise.[47] At week 52, all subjects were re-randomized to either placebo or lorcaserin for an additional year. At 1 year, ITT-LOCF analysis showed that obese subjects lost 3.6 kg more than controls (3.6%). At 1 year, 47% of the subjects receiving lorcaserin showed a weight loss >5%, as compared to 20.5% in the control group. In the lorcaserin group, 22.6% of the subjects showed a weight loss >10% as compared to 7.7% in the control group. After the first year, subjects on lorcaserin were either maintained on the drug or switched to placebo. Subjects who showed >5% weight loss during year 1 and were maintained on lorcaserin treatment in year 2 were able to maintain their weight loss better than those who had been switched to placebo (67.9% vs. 50.3%). The most frequent side effects noted in the trial included headache, dizziness, and nausea, but there were no significant differences between the treatment and placebo groups with regard to serious adverse events.

In a second phase III trial, BLOSSOM, 4,008 subjects were treated with lorcaserin 10 mg, either daily or b.i.d., for 1 year.[48] After 1 year, ITT-LOCF analysis showed that the lorcaserin 10 mg b.i.d. group achieved a 3.1% placebo-adjusted weight loss. The percentage of lorcaserin-treated subjects achieving >5% weight loss was 47.2% vs. 25% in the control group. The corresponding percentages of those achieving >10% weight loss were 35.1 and 16.1% in the two groups, respectively.

Other end points evaluated in the BLOOM trial included significant placebo-adjusted changes in HbA_{1c} (−0.07%), total cholesterol (−1.5%), blood pressure (−0.6 mm Hg systolic, −0.5 mm Hg diastolic), plasma triglycerides (−6.0%), and heart rate (−0.4 bpm). However, no significant improvements in these parameters were seen in the BLOSSOM trial. The rates of new valvulopathy (as defined by the FDA) in BLOOM were 2.7% in the lorcaserin 10 mg–twice-daily group and 2.3% in the placebo group at week 52 and 2.6 and 2.7% in the two groups, respectively, at week 104. In BLOSSOM, the rates of new valvulopathy at week 52 were 2.0% in the lorcaserin 10 mg–twice-daily group, 1.4% in the lorcaserin 10 mg–once-daily group, and 2.0% in the placebo group.

Major adverse events in both BLOOM and BLOSSOM included headache (15.6% vs. 9.2% in controls), nausea (9.1% vs. 5.3% in controls), dizziness (8.7% vs. 3.9% in controls), fatigue, and dry mouth. There was no evidence of lorcaserin-induced anxiety or depression.

A final trial, the BLOOM-DM, was conducted in patients with DM but was designed mainly to evaluate weight loss. The trial included 604 DM patients who were overweight or obese . They were randomized to receive lorcaserin 10 mg twice daily, lorcaserin 10 mg once daily, or placebo. The three primary efficacy end points at week 52 were the percentage of patients who lost ≥5% of their baseline body weight, change in body weight from baseline, and the percentage of patients who lost ≥10% of their baseline body weight. Per MITT-LOCF analysis, lorcaserin 10 mg twice daily met the three primary efficacy end points by producing significant weight loss relative to placebo (*P* < 0.0001). At week 52, 37.5% of patients treated with lorcaserin 10 mg twice daily showed a weight loss of ≥5%, which was more than twice the percentage in the placebo group (16.1%). Patients treated with lorcaserin 10 mg twice daily had a mean weight loss of 4.5% (4.7 kg) as compared with 1.5% (1.6 kg) in the placebo group. Also, at week 52, 16.3% of patients treated with lorcaserin 10 mg twice daily achieved a weight loss ≥10%, as compared with 4.4% of patients taking placebo.

The BLOOM-DM trial also evaluated multiple secondary end points at week 52: glycemic and lipid levels, blood pressure, body composition, and quality of life. Data for the first three of these parameters are available: those on lorcaserin 10 mg twice daily showed a reduction of 0.9% in HbA_{1c} as compared with a 0.4% reduction in the placebo group (*P* < 0.0001); however, changes induced by lorcaserin treatment (relative to placebo) in levels of fasting insulin, triglycerides, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein (LDL) cholesterol, and systolic and diastolic blood pressure were not statistically significant.[49] A finding that caused some concern was a higher rate of new valvulopathy (as seen in echocardiography) associated with lorcaserin than with placebo. At week 24, 2.5% of patients taking lorcaserin 10 mg twice daily and 1.9% of those on placebo had evidence of new valvulopathy. At week 52, these figures were 2.9% and 0.5%, respectively.

In September 2010, an FDA advisory panel voted to recommend against granting approval to market the drug. This was on the basis of concerns over both safety and efficacy. In October 2010, the FDA stated that it that it could not approve the application for lorcaserin in its present form.[50] The panelists were concerned about unexplained preclinical carcinogenicity signals in rats, specifically, an increase in breast tumors with lorcaserin. Second, there were concerns regarding the rates of new valvulopathy. The panelists suggested that lorcaserin could eventually be approved if some unanswered questions about the risks of the drug could be resolved. In January 2011, the manufacturer of the drug (Arena) announced that it is continuing discussions with the FDA to finalize protocols for action designed to address the

issues raised by the FDA, and that it hopes to resubmit the new drug application for lorcaserin by the end of 2011.[51]

Liraglutide

Glucagon-like peptide-1 (GLP-1) analogs are being increasingly studied for their role in body-weight control given their growing role in the weight-centric management of Type 2 diabetes. Weight-centric management of diabetes recognizes the importance of reducing body weight, as well as blood glucose, as a goal of diabetes management. GLP-1 is a humoral gut peptide that enhances insulin secretion, and the currently available analogs have been approved for the treatment of diabetes. GLP-1 also delays gastric emptying and suppresses appetite, resulting in decreased energy intake and weight loss.[52]

Studies showed that exenatide (a GLP-1 analog) given twice daily to diabetics not only lowered HbA_{1c} but also led to a dose-related reduction in body weight at 30 weeks (2.9 kg vs. 0.3 kg for placebo).[53] Liraglutide, a long acting GLP-1 analog marketed as Victoza, was approved in January 2010 for the treatment of diabetes.

In a double-blind, placebo-controlled, open-label trial of liraglutide, 564 subjects with (BMI 30–40 mg/m^2) were randomly assigned to receive orlistat (120 mg t.i.d.), one of four dosage regimens of liraglutide (1.2 mg, 1.8 mg, 2.4 mg, or 3.0 mg), or placebo.[54] All subjects were also placed on a diet resulting in a 500 kcal per day energy deficit. Intention-to-treat analysis demonstrated that subjects lost significantly more weight with liraglutide than with placebo, and that this weight loss was dose-dependent. The mean weight loss with liraglutide was 4.8 kg at the lowest dose (1.2 mg liraglutide), and 5.5, 6.3, and 7.2 kg, respectively, for each increase in dosage. The weight loss with orlistat was 4.1 kg, and with placebo it was 2.8 kg. Of the patients receiving liraglutide 3.0 mg, 76% lost >5% of their weight, as compared to 44% in the orlistat group and 30% in the placebo group. All doses of liraglutide were followed by a reduction in blood pressure and a reduction was seen in the prevalence of prediabetes (84–96% reduction) at dosages of 1.8–3.0 mg per day. The prevalence of nausea and vomiting were greater in individuals on liraglutide than in those on placebo, but adverse events were mainly transient and rarely led to discontinuation of treatment.

Novo Nordisk plans to initiate additional phase III trials of liraglutide for antiobesity treatment in 2011.

Cetilistat

Cetilistat is an inhibitor of pancreatic lipase, an enzyme that breaks down triglycerides in the intestine. Without this enzyme, triglycerides from the diet are prevented from being hydrolyzed into absorbable free fatty acids and are left to be excreted undigested. This drug, while similar to the currently FDA-approved drug orlistat, is thought to have a more tolerable side-effect profile because of the difference in the molecular structure of the drug.

In a phase IIb trial, 612 obese, diabetic patients were randomized to receive cetilistat (40, 80, or 120 mg), orlistat (120 mg), or placebo.[55] Over a 12-week treatment period, cetilistat 80 and 120 mg promoted significant weight loss relative to placebo

(3.85 kg and 4.32 kg, respectively, vs. 2.86 kg for placebo), thereby meeting the trial's primary end point. Cetilistat-induced weight loss was similar to that achieved with orlistat (3.78 kg). The rates of premature discontinuation due to adverse events were 2.5, 5.0, and 2.5% for the cetilistat 40, 80, and 120 mg arms, respectively. The comparable figures for orlistat and placebo were 11.6 and 6.4%, respectively. Given that orlistat's gastrointestinal side effects are a principal cause for discontinuation, cetilistat may become a preferred lipase inhibitor for achieving weight loss. Phase III trials of cetilistat are currently under way in Japan.

Tesofensine

Tesofensine is a triple monoamine reuptake inhibitor that blocks the reuptake of serotonin, dopamine, and noradrenaline but does not interact with monoamine receptors. Originally, this drug was developed for the treatment of Alzheimer's and Parkinson's diseases, and it was noted in clinical trials that there was a persistent weight loss among patients. The drug is believed to induce weight reduction through both appetite suppression and increased thermogenesis.[56]

A phase II proof-of-concept study was conducted by Astrup and colleagues. This randomized, double-blind, placebo-controlled study enrolled 203 subjects with baseline BMI 30–40 kg/m^2. The subjects were randomized to receive 24 weeks of treatment with tesofensine 0.25, 0.5, or 1 mg, or placebo, after a 2-week run-in period. ITT-LOCF analysis demonstrated that the weight reductions were dose-dependent. The tesofensine 0.25, 0.5, and 1 mg doses achieved placebo-adjusted weight losses of 4.7, 9.1, and 10.6 kg, respectively.[57]

Adverse side effects of tesofensine include dry mouth, nausea, dizziness, constipation, and abdominal pain. The drug is relatively well tolerated; 71% of subjects on the highest dose completed the trial and 20% withdrew because of adverse events. There was, however, some concern over possible cardiovascular side effects. There was a notable dose-dependent increase in heart rate up to 8.5 bpm at the highest dose (1.0 mg). In addition, there was a 1–2 mm Hg increase in blood pressure that was not statistically significant.

Given these findings, further phase III trials might limit the dose to 0.25 and 0.5 mg so as to reduce the impact on heart rate and blood pressure.

Velneperit

In the 1980s, neuropeptide Y (NPY) was established as a potent orexigen.[58] NPY stimulates food intake, inhibits energy expenditure, and increases body weight by activating the hypothalamic NPY receptors Y1 and Y5.[59] The levels are temporally related to food intake and are elevated with energy depletion.

Velneperit, a once-daily, oral neuropeptide Y5 receptor antagonist, blocks the binding of centrally acting NPY to its Y5 receptor, thereby controlling energy balance and food consumption. In February 2009, Shionogi reported the results of two phase II studies of velneperit. The trials enrolled 1,566 obese patients and evaluated the efficacy and safety of two doses (800 mg and 1,600 mg) relative to placebo, alongside a reduced-calorie diet (RCD) or a low-calorie diet (LCD).[60]

In the RCD study, 656 subjects with obesity (BMI 30–45 kg/m^2) were first put on a 6-week reduced-calorie diet regimen (800 kcal/day). Upon completion of these 6 weeks, they were randomized to receive 800 or 1,600 mg of velneperit once daily, or placebo, in conjunction with the same 800 kcal/day diet for an additional 54 weeks. MITT-LOCF analysis showed that the subjects who received 800 mg velneperit lost an average of 3.8 kg of body weight vs. 0.8 kg in the placebo group ($P < 0.0001$). The percentages of patients who lost >5% of their initial body weight were 35% in the treatment group (800 mg) vs. 12% in the placebo group. Shinogi notes that the weight loss relative to placebo was statistically significant in both treatment groups (both doses of velneperit); however, the study did not report the values for the higher-dose treatment group.

In the LCD study, 771 obese subjects (BMI 30–45 kg/m^2) were immediately randomized to one of three groups: (i) a placebo/placebo group, i.e., placebo in conjunction with a fixed LCD of 950 kcal/day for 6 weeks, followed by placebo and an RCD (800 kcal/day) for the remaining 54 weeks; (ii) a placebo/velneperit group, i.e., LCD/placebo for 6 weeks followed by 1,600 mg of velneperit/RCD for the remaining 54 weeks; or (iii) a velneperit/velneperit group, i.e., 1,600 mg velneperit in combination with the LCD for 6 weeks, followed by 54 weeks of 1,600 mg velneperit plus the RCD. Using MITT-LOCF analysis, Shinogi reported that both velneperit treatment groups demonstrated statistically significant reductions in body weight as compared to placebo. The treatment group with the strongest performance was the placebo/velneperit group, in which subjects lost 7.1 kg of their baseline weight vs. 4.3 kg in the placebo/placebo group ($P < 0.0001$). It was also reported that 52% of the placebo/velneperit group and 35% of the placebo/placebo group lost >5% of their initial body weight.

Preliminary data from the study showed that velneperit met the primary end point of weight reduction as well as the secondary end points of improving serum lipid levels and reducing waist circumference.

In terms of safety, the overall rate of withdrawal of subjects from the study because of treatment-related adverse events was 7% across both treatment groups as well as the placebo group in the RCD study. In the LCD study, the withdrawal rate was 5% for placebo/placebo, 7% for placebo/velneperit, and 10% for velneperit/velneperit. The most frequent adverse events were nasopharyngitis, upper-respiratory infections, sinusitis, and headache. Laboratory data also show mild decreases in hematocrit, hemoglobin, and red blood cell count, although all of these remained within the normal ranges.

Shinogi has completed the phase II trials, and planning for phase III trials is under way.

Obinepitide

Obinepitide is a synthetic analog of two naturally occurring human hormones: PYY3-36 and pancreatic polypeptide. These hormones are normally released during a meal and are known to play a role in the regulation of food intake and appetite, acting as satiety signals. Initial studies in humans have shown that infusion of PYY3-36 reduced food intake in both obese and lean subjects, besides reducing perceived hunger prior to a meal.[61]

Obinepitide's unique characteristic is that it targets both the Y2 and Y4 receptors without showing an affinity for the Y1 receptor, which is associated with cardiovascular side effects. In March 2006, 7TM Pharma announced positive results from obinepitide's proof-of-concept phase I/II study. Subcutaneous injections of once- and twice-daily obinepitide were well tolerated and inhibited food consumption for up to 9 h after dosing relative to placebo.[62] Obinepitide remains under development.

EARLY-PHASE DRUGS (PHASE I)
TTP435

Agouti-related protein (AgRP) is a neuropeptide produced in the arcuate nucleus of the hypothalamus. It is coexpressed with NPY and works by increasing appetite and decreasing metabolism and energy expenditure.[63]

TransTech Pharma identified TTP435 as a potent and selective inhibitor of AgRP. TTP435 has been assessed in a series of *in vitro* and *in vivo* studies as proof of concept to demonstrate the value of inhibiting AgRP as a safe and effective treatment of obesity.[64] *In vivo*, TTP435 is orally bioavailable, with high brain penetration. In several studies of animal models of obesity ranging in duration from overnight administration to 4-week treatment, TTP435 was shown to reduce food intake and body weight gain, reduce fat composition, and reduce insulin levels in a dose-dependent fashion. TTP435 is currently being assessed in obese subjects in phase II clinical trials.

ZGN-433

ZGN-433 is a methionine aminopeptidase 2 inhibitor. The mechanism through which it effects weight loss in obesity is unclear. Originally developed as a treatment for solid tumors, it was initially thought to block angiogenesis (similar to cancer treatment) and reduce adipose tissues by blocking blood supply. However, preliminary studies did not confirm this theory. They did show, however, that administration of the drug caused profound weight loss in mice, which thereafter achieved ideal body weight. The drug may play a role in altering the mechanism by which the body metabolizes fat. In dogs receiving ZGN-433, weight loss is associated with improved glycemic control and an apparent reduction in demand for insulin secretion. In humans, an effective dose was associated with improved lipid profiles: LDL cholesterol and triglycerides were reduced by 23–38%, beyond what would be anticipated by weight loss alone. Blood pressure was not increased by treatment with this compound.

In January 2011, Zafgen reported positive results from its phase Ib study using ZGN-433.[65] A double-blind, placebo-controlled, multiple-ascending-dose study was performed in women with BMI 32–35 kg/m^2, with 24 subjects enrolled in the core study. The primary objective was to evaluate the safety and tolerability of the compound. The second objective was to obtain information on weight loss in subjects exposed to eight doses of IV ZGN-433 administered over 4 weeks. The subjects received ZGN-433 twice weekly for a total of eight doses at three dosage levels (0.22, 0.65, and 1.96 mg per administration). Subjects receiving ZGN-433 had a reduction in median body weight of 1 kg per week and 3.1% of initial body weight over

26 days, relative to placebo. In addition, there was a decline in hunger, a 38% reduction in triglyceride levels, and a 23% reduction in LDL cholesterol. In addition, β-hydroxybutyrate, an indicator of fat oxidation, increased to levels seen with very-low-energy diets.

Zafgen plans to initiate phase IIa studies in 2011.

PP 1420

PP 1420 is a pancreatic polypeptide analog that is thought to increase satiety. Previous studies of PP have shown that injections of human PP have the effect of reducing appetite and food intake. Human PP has a very short half-life. PP 1420 is a synthetic form of PP with a longer half-life. Phase I trials have been completed by Wellcome Trust, but the results have not yet been released.[66]

GSK 598809

GSK 598809 is a D3 antagonist that blocks dopamine. It is thought that blocking dopamine may reduce the intake of foods high in fat and sugar, and may be a potential treatment option for compulsive overeaters and/or binge eaters. The medication is being developed for the treatment of substance dependence and other impulsive disorders. GlaxoSmithKline is currently completing a phase I fMRI study designed to examine the behavioral and physiological effects of a single dose of the D3 antagonist on food reward and reinforcement in relation to food-seeking behavior under conditions of fasting, using neurocognitive and metabolic end points in subjects with obesity. The study was scheduled to be completed in mid-2011; no further data have been released.

AZD7687

Diglyceride acyltransferase (DGAT), or *O*-acyltransferase, catalyzes the formation of triglycerides from diacylglycerol and acyl-CoA. The reaction catalyzed by DGAT is considered the terminal and only committed step in triglyceride synthesis and to be essential for the formation of adipose tissue.[67] Because the ability to make triglycerides is essential for the accumulation of adipose tissue, inhibition of triglyceride synthesis may ameliorate obesity and its related medical consequences. Acyl coenzyme A (CoA): diacylglycerol acyltransferase 1 (DGAT1) is one of two DGAT enzymes that catalyze the final reaction in the known pathways of mammalian triglyceride synthesis.

Mice lacking DGAT1 are resistant to obesity and have increased sensitivity to insulin and leptin.[68] DGAT1-deficient mice are also resistant to diet-induced hepatic steatosis. The effects of DGAT1 deficiency on energy and glucose metabolism result, in part, from the altered secretion of adipocyte-derived factors. Although complete DGAT1 deficiency causes alopecia and impairs development of the mammary gland, these abnormalities are not observed in mice with partial DGAT1 deficiency. These findings suggest that pharmacological inhibition of DGAT1 may be a feasible therapeutic strategy for human obesity and DM.[69]

AstraZeneca had planned to complete its phase I study of AZD7687 in February 2011.

Ezlopitant

Ezlopitant is a neurokinin receptor-1 antagonist that has been implicated in both learned appetitive behaviors and addiction to alcohol and opioids. Recent evidence from rodent studies suggests that ezlopitant reduces the appetite for sucrose, thereby decreasing the consumption of sweetened foods and drinks.[70] It has been suggested that sweet foods and drinks can be addictive in the same way as alcohol; this drug may therefore have a role in obesity treatment. Further studies have yet to be done.

Thyroid hormone receptor agonists

Thyroid hormone receptor (TR) agonists have been under investigation as potential targets for treating obesity. Thyroid
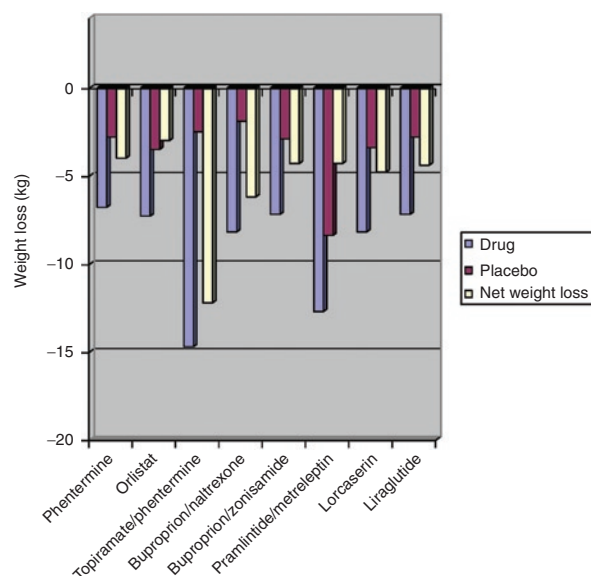
Figure 1 Expected weight loss observed with currently approved and investigational drugs.

Table 4 Expected weight loss with currently approved and investigational drugs

Agent	Drug	Placebo	Net weight loss
Phentermine	6.8 kg	2.8 kg	4.0 kg
Orlistat	7.3 kg	3.5 kg	3.0 kg
Topiramate	4.5 kg	1.7 kg	2.8 kg
Bupropion	6.0 kg	2.8 kg	3.2 kg
Topiramate/phentermine	14.7 kg	2.5 kg	12.2 kg
Bupropion/naltrexone	8.2 kg	1.9 kg	6.2 kg
Bupropion/zonisamide	7.2 kg	2.9 kg	4.3 kg
Pramlintide/metreleptin	12.7 kg	No placebo	12.7 kg (vs. No placebo)
Lorcaserin	8.2 kg	3.4 kg	4.8 kg
Liraglutide	7.2 kg	2.8 kg	4.4 kg
Cetilistat	4.3 kg	2.8 kg	1.5 kg
Tesofensine	11.2 kg	2 kg	9.2 kg
Velneperit	7.1 kg	4.3 kg	2.8 kg

hormone is a highly metabolic molecule that increases energy expenditure and lowers serum cholesterol and triglycerides. It is known to act at two receptors: TRα and TRβ. TRα receptors are found in the heart, brain, and bone, and contribute to the undesirable side effects of thyroid hormone activation, including cardiac arrhythmias, bone loss, and nervousness.[71] TRβ is thought to be responsible for the metabolic role in both liver and adipose tissue. TRβ-selective agonists have been developed that achieve beneficial metabolic effects while avoiding the undesirable side effects of TRα pathway activation. GC-1, a selective TRβ agonist, when administered to rats, demonstrated a normalization of serum cholesterol and triglyceride levels. In addition, GC-1 was found to accelerate energy expenditure in rats and lower body weight in primates without cardiac side effects.[72] The accelerated metabolic rate was followed by a decrease in fat but not in lean mass. In other studies, KB2115, a selective TRβ agonist, was administered to moderately overweight and hypercholesterolemic human subjects. It was found to be safe and well tolerated, and it caused a 40% lowering of both total and LDL cholesterol. Phase II trials are under way to investigate the efficacy of TRβ receptor agonists in treating dyslipidemia, but they may become a potential target for antiobesity treatment in the near future.

CONCLUSIONS

The vast gap in the current pharmacological treatment options for obesity is surprising given the high prevalence and economic burden of obesity. Many factors have mitigated against active drug development, including the poor safety and efficacy of previous antiobesity drugs. However, compelling targets are now on the horizon (**Table 4** and **Figure 1**). The new generation of antiobesity drugs offers hope for the management of obesity, although no single agent is likely to be a panacea. If sustained success is to be achieved, obesity will need to be managed like many other chronic diseases, with combination therapies and long-term treatment.

CONFLICT OF INTEREST

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