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ORIGINAL ARTICLE

ANTI-OBESITY DRUGS: PRESENT AND FUTURE

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ABSTRACT: The ideal anti-obesity drug would produce sustained weight loss with minimal side effects. The mechanisms that regulate energy balance have substantial built-in redundancy, overlap considerably with other physiological functions, and are influenced by social, hedonic and psychological factors that limit the effectiveness of pharmacological interventions. It is therefore unsurprising that anti-obesity drug discovery programmes have been littered with false starts, failures in clinical development, and withdrawals due to adverse effects that were not fully appreciated at the time of launch. Drugs that target pathways in metabolic tissues, such as adipocytes, liver and skeletal muscle, have shown potential in preclinical studies but none has yet reached clinical development. Recent improvements in the understanding of peptidergic signalling of hunger and satiety from the gastrointestinal tract mediated by ghrelin, cholecystokinin (CCK), peptide YY (PYY) and glucagon-like peptide-1 (GLP-1), and of homeostatic mechanisms related to leptin and its upstream pathways in the hypothalamus, have opened up new possibilities. Although some have now reached clinical development, it is uncertain whether they will meet the strict regulatory hurdles required for licensing of an anti-obesity drug. However, GLP-1 receptor agonists have already succeeded in diabetes treatment and, owing to their attractive body-weight-lowering effects in humans, will perhaps also pave the way for other anti-obesity agents. To succeed in developing drugs that control body weight to the extent seen following surgical intervention, it seems obvious that a new paradigm is needed. In other therapeutic arenas, such as diabetes and hypertension, lower doses of multiple agents targeting different pathways often yield better results than strategies that modify one pathway alone. Some combination approaches using peptides and small molecules have now reached clinical trials, although recent regulatory experience suggests that large challenges lie ahead. In future, this polytherapeutic strategy could possibly rival surgery in terms of efficacy, safety and sustainability of weight loss.

KEYWORDS: Obesity, GLP-1 receptor agonist, Orlistat.

INTRODUCTION: Obesity, most often defined as a body mass index (BMI) of ≥30 kg/m^2 and caused by an imbalance between energy intake and expenditure, is widely recognized as the largest and fastest growing public health problem in the developed and developing world. Prevalence of the disorder in adults has more than tripled in the past decade, and obesity currently affects approximately 30–35% of the general population in the USA and 25% in the UK. It has been estimated that, in 2005, some 400 million adults worldwide were obese, with a total of 1.6 billion being overweight.

The incidence of obesity is increasing dramatically to epidemic proportions in virtually all societies of the world and with it come the major pathological consequences including hypertension, type-2 diabetes,[1] osteoarthritis, dyslipidemia and cancers.[2] Many of these diseases can be prevented or ameliorated with a reduction in body weight.[3] Despite dramatic advances in our understanding of

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central regulation of energy balance and obesity, there are very few approved anti-obesity pharmacological treatments and their modest efficacy and safety concern value.[4] The European union regulatory authorities suggest that efficacy be based upon achieving a mean weight loss of 10% from the baseline after 1 year of treatment. The US FDA requires that more than 5 % placebo subtracted weight loss difference after 1 year is needed and 35% of treated patients should double the proportion of placebo treated patients.[5] In the Swedish obese subject study, the incidence of new cases of DM was reduced to zero over a period of 2yrs in patients who lost more than 12% of their weight, in contrast the incidence of new cases of DM was 8.5% in those who did not lose any weight. Despite rigorous attempts at behavioral change, many patients are unable to achieve long term maintenance of weight loss through lifestyle alone and the growing number of patients forced to undergo bariatric surgery points the need for effective drug treatments.[5] Hence there is need of continuous dialogue between obesity researchers, pharmaceutical industry band regulatory authorities to stimulates research and drug development based upon the clinical need of the patients and recognizing the true clinical endpoints should be the priority so as to allow appropriate risk: benefit assessment.[5]

Centrally acting sympathomimetics, such as the amphetamine derivatives desoxyephedrine, phentermine and diethylpropion, were among the earliest pharmacological agents used for weight loss. They were popular in the 1950s and 1960s, but growing concerns about cardiovascular risk and abuse potential led to a marked decline in their use by the early 1970s. Although still available in many countries, phentermine and diethylpropion were largely superseded by the serotonin (5-HT)-releasing agents fenfluramine and dexfenfluramine. It was known from the outset that agents of this series had the potential to produce primary pulmonary hypertension, but the risk was deemed sufficiently low against the weight loss benefits. However, within only a few years, reports of cardiac valvulopathy, particularly when these agents were combined with phentermine, led the manufacturers to withdraw fenfluramine and dexfenfluramine from the market.[6,7]

Until very recently, three agents were approved in Europe for the long-term clinical management of obesity and related metabolic syndrome: sibutramine, rimonabant and orlistat. Sibutramine, a dual monoamine (Noradrenaline and serotonin)-reuptake inhibitor, was introduced to clinical practice in the late 1990s and is believed to achieve very modest weight loss by decreasing energy intake and increasing energy expenditure.[8] There is substantial evidence that phytocannabinoids (i.e. cannabis and its constituents) and endocannabinoids (e.g. anandamide) stimulate appetite in animals and humans, and that these effects are mediated via cannabinoid CB1 receptors in the brain or periphery. Rimonabant, a cannabinoid CB1 receptor antagonist/inverse agonist developed in the mid-1990s, suppresses appetite and weight gain in experimental animals. However, by October 2008, burgeoning reports of serious psychiatric problems (such as anxiety, depression and suicide) led to suspension of marketing authorisations. This decision in turn rapidly led to the termination of several CB1-receptor-antagonist-based anti-obesity drug development programmes [including those for rimonabant, taranabant, otenabant, surinabant and ibipinabant.[9] Phentermine, approved in 1959 by US-FDA, was the most commonly prescribed antiobesity agent in the United States. Orlistat, 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.[10] Historically, the limitations have been due to a variety of concerns 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.[11,12]

Hypothalamus and the Central Control of Feeding and Energy Homeostasis: The hypothalamus is the key processing area within the brain for the integration of numerous signals related to energy homeostasis. Peripheral signals of satiety are integrated and passed on to other areas of the brain via nuclei in the hypothalamus. Peripheral signals from adipose stores, the gastrointestinal tract and endocrine system influence the activity of neurons within the arcuate nucleus of the hypothalamus. When fat stores are reduced and energy levels are low, hunger signals mediated via an increase in the gut hormone, ghrelin, and reductions in insulin, glucose, leptin and cholecystokinin (CCK) cause increases in the activity of both neuropeptide Y (NPY) and agouti-related protein (AgRP) neurons, which in turn leads to decreased activity of the melanocortin system, leading to disinhibition of melanin concentrating hormone (MCH) and orexin (ORX) signalling producing a marked orexigenic effect. Following a meal the reverse occurs, with high levels of glucose, insulin, CCK and reduced ghrelin levels leading to increases in pro-opiomelanocortin (POMC), in turn increasing α-melanocyte stimulating hormone (α-MSH) release and decreasing MCH/ORX activity, leading to satiation and a termination of feeding.[13,14]

Combination Therapy: Qnexa It consist of lower doses of topiramate and phentermine. 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. Topiramate is a weak carbonic anhydrase inhibitor, inhibits isoforms II and IV; it also modulates GABA-A receptors which causes inactivation of Na-channels. The modulation of γ-aminobutyric acid may have a role in the reduction of food intake.[9] The rational for combining topiramate with phentermine is to minimise the required dose of each of the medication thereby opening up more than one pathway to satiety in hope of achieving greater efficacy.[15]

In Oct. 2010, the FDA did not approved Qnexa in its current form and requested more evidence that the elevated heart rate associated with its use, does not increase cardiovascular risk. FDA also had concern regarding the teratogenic potential of drug.[16] In Jan. 2011 VIVUS announced that FDA had requested additional information regarding teratogenecity and company will continue to work with FDA in an effort to secure approval. VIVUS has completed three Phase III studies of Qnexa.[17]

Contrave A dual antiobesity agent. It is combination of bupropion and naltriaxone. Buproprion is inhibitor of DA and NA used for treating depression and inducing smoking cessation. During initial trials it was noted that it suppressed appetite and food craving. Monotherapy with bupropion shown weight loss of 2.8 kg at 52 weeks as single agent and this does not meet FDA criteria for an antiobesity drug.[10] As monotherapy naltriaxone is associated with minimal weight loss.[3]Thus one would not predict that combining these two agents would associate with clinically meaningful and sustained pattern of weight reduction.[18]

In 2009, Greenway et al conducted a double-blind placebo controlled study, enrolling 419 obese subjects BMI 30–40kg/m^2g over a period of 24 weeks. The subjects were receiving one of the

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following: placebo, naltrexone 48mg alone, bupropion slow-release (SR) 400mg alone, or combinations of bupropion 400mg with varying doses of naltrexone (16mg, 32mg, and 48mg).[11]

At 24 weeks, the average weight loss in each of the groups was as, 0.9kg 1.1kg; 2.6kg; for alone drug. With 400mg bupropion/16mg, 32mg, 48mg naltrexone, 5.1kg; 5.1kg, and 4kg respectively. At a 48-week extension time point, the weight loss increased to 7.4kg, 8.2kg, and 10kg, respectively, in the three combinations treatment groups. These data endorse the hypothesis that two drugs working synergistically and in combination provide greater weight loss than either of them singly.[19,20] 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.

Empatic is the combination drug of zonisamide and bupropion. Clinically, it has been shown to induce weight loss as a side effect. However, a possible mechanism is sodium channel modulation and enhancement of dopamine and serotonin neurotransmission, potentially resulting in weight loss.[21] Bupropion, has also been linked to weight loss. 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.[12] The addition, it was thought that bupropion when added to zonisamide decreases the depressive and sedative properties associated with zonisamide while the latter might reduce the likelihood of bupropion induced seizures.[22]

In September 2009, Orexigen released data from a 24-week phase IIb double-blind, placebo-controlled trial of Empatic in 729 obese patients with BMI range 27–45kg/m.[2] The patients were randomized to one of six arms: Two groups : 1) bupropion IR 360mg + zonisamide SR 120 mg 2) bupropion IR 360mg + zonisamide SR 360mg. Three single-treatment groups 1) bupropion IR 360mg, 2) zonisamide SR 360mg, 3) zonisamide SR 120 mg and 4) placebo.[23]

The combination therapy containing zonisamide 120 mg, 360mg given weight loss of 6.1% and 7.5%. Both of these combinations produced weight-loss effects that were significantly superior to that of placebo and also superior to the zonisamide monotherapy. 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. The plans for phase III Empatic trials have not yet been announced.[24]

Pramlintide 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, 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 obese individuals. Amylin is a peptide hormone with both glucose-regulatory and anorexigenic actions. Amylin is stored in the pancreatic A-cell secretory vesicles and secreted in response to food intake. It acts in the hindbrain area postrema and central nucleus of the amygdala to reduce food intake, by acting as a satiety signal.[2] Clinical studies have shown that pramlintide (Synthetic amylin) 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.[25]

The results of mechanistic studies in rats pre-treated 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.

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In a 28-week, double-blind, placebo-controlled study enrolled 608 obese BMI 27–45 kg/m.[2] After a 1-week placebo lead-in period, the subjects were randomized to twice-daily therapy with eight regimens: (i) placebo + placebo, (ii) pramlintide 360µg + placebo, (iii) metreleptin 5mg + placebo, (iv) pramlintide 180µg + metreleptin 2.5 mg, (v) pramlintide 180µg + metreleptin 5µg, (vi) pramlintide 360µg + metreleptin 1.25mg, (vii) pramlintide 360µg + metreleptin 2.5mg, or (viii) pramlintide 360 µg + metreleptin 5mg. The magnitude of the weight loss was found to be dependent on dose and baseline BMI. Treatment with the highest pramlintide + metreleptin doses had an average weight loss of 11% ($P < 0.01$), when compared with placebo group (1.8%) and in the groups that received either of the agents singly (5%).[26]

Monotherapy in Phase II/III Trials: Lorcaserin It is a 5-HT receptor agonist. 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 seen that 5HT-2A receptors are hallucinogenic.[14] Whereas 5HT-2B receptor activation is associated with the development of valvulopathy and primary pulmonary hypertension. Lorcaserin have a high affinity for the 5HT-2C subtype and very less for 5HT-2A and 5HT-2B; hence become a target of interest. 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 receive lorcaserin 10 mg twice daily, lorcaserin 10 mg once daily, or placebo. The results with lorcaserin 10mg twice daily had a mean weight loss of 4.5% as compared with 1.5% in the placebo group. 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 January 2011, the manufacturer of the drug announced that 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.[27]

Liraglutide Glucagon-like peptide-1 (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. Exenatide and liraglutide are FDA approved GLP-1 analog given DM. In a double-blind, placebo-controlled 20-week trial, with open-label orlistat comparator in 19 sites in Europe. 564 individuals were randomly assigned, to one of four liraglutide doses (1·2mg, 1·8mg, 2·4mg, or 3·0mg, n=90—95) or to placebo (n=98) administered once a day subcutaneously, or orlistat (120 mg, n=95) three times a day orally. All individuals had a 500 kcal per day energy-deficit diet, including the 2-week run-in. An 84-week open-label extension followed.[28]

Mean weight loss with liraglutide 1·2-3·0mg was 4·8kg, 5·5kg, 6·3kg, and 7·2kg compared with 2·8kg with placebo and 4·1kg with orlistat, Nausea and vomiting occurred more often in individuals on liraglutide than in those on placebo, but adverse events were mainly transient and rarely led to discontinuation of treatment. This is not going to be a general slimming agent, but rather one that is fulfilling a true medical need in the field of medical obesity - where people are either very obese, or are obese and have pre-diabetes or other metabolic disturbances," Krogsgaard said. Victoza is a once-daily version of the new-generation GLP-1 type of drug which stimulates cells to release insulin when blood sugar levels are high.[29]

Novo Nordisk expects to outline the clinical development strategy for semaglutide, a once-weekly GLP-1 analogue, and the once-weekly version of liraglutide in the second half of 2011,"

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Semaglutide, which is based on a different molecule than Victoza, has finished phase II trials. The once-weekly version of Victoza is in the pre-clinical stage. Taspoglutide, under development by Roche Holding AG and Ipsen SA, is another GLP-1 drug for type-2 diabetes.[16] Based on the feedback from the FDA, Novo Nordisk now plans to re-initiate the global phase 3 programme in the first half of 2011 in clinical trials comprising approximately 5,000 patients. The re-initiation of liraglutide obesity trials underlines Novo Nordisk's dedication to the development of the liraglutide portfolio that is the cardiovascular outcomes trial for Victoza, the obesity programme, the fixed-ratio combination of insulin degludec and liraglutide, and finally a once-weekly version of liraglutide. Novo Nordisk remains committed to the development of a longer-acting GLP-1 analogue and now expects to outline the clinical development strategy for semaglutide, a once-weekly GLP-1 analogue, and the once-weekly version of liraglutide in the second half of 2011. Victoza lowers blood glucose by stimulating the release of insulin and lowering of glucagon secretion when blood sugar levels are high and also by slowing gastric emptying. Victoza also reduces body weight and body fat mass through mechanisms involving reduced hunger and lowered energy intake. Victoza is a once-daily injection taken any time of day independent of meals.[30]

Cetilistat: Cetilistat is an inhibitor of pancreatic lipase, an enzyme that breaks down triglycerides in the intestine. This drug, is similar to the currently FDA-approved drug orlistat. 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. Evidence of the safety and efficacy of cetilistat has been established through extensive Phase I and Phase II clinical trials in Europe, the US and Japan in over 1,000 subjects (over 800 subjects on active drug). In a second Phase IIb study involving 612 clinically obese diabetic patients, along with weight loss Cetilistat was also shown to cause statistically significant reductions in HbA1c. Furthermore, the proportion of subjects discontinuing treatment for adverse events was lower with cetilistat than with placebo and with Orlistat, confirming earlier studies showing that cetilistat has a superior tolerability profile. Cetilistat has begun a Phase III trial in Japan.[31]

Tesofensine: Tesofensine is a triple monoamine reuptake inhibitor that blocks the reuptake of 5HT, DA, and NA. 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. 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. Analysis demonstrated that the weight reductions were dose-dependent. The weight losses of 4.7, 9.1, and 10.6 kg, respectively. Adverse effects of tesofensine include dry mouth, nausea, dizziness, constipation, and abdominal pain. The drug is relatively well tolerated. 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.[12] In vitro, the compound potently blocked dopamine, norepinephrine and serotonin reuptake. A notable occurrence of unintended weight loss

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was observed in individuals treated with the drug. Preclinical data from diet-induced obese rats supported the hypothesis that tesofensine reduces body weight. In phase II clinical trials with tesofensine in obese individuals, dose-related reductions in body weight, body fat and waist circumference, as well as improvements in other obesity-related endocrine factors, were observed. FDA recently launched ph. III programme for tesofensine.[32]

Velneperit: NPY (neuropeptide Y) stimulates food intake, inhibits energy expenditure, and increases body weight by activating the hypothalamic NPY receptors Y1 and Y5. 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 the RCT 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. 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 ($P < 0.0001$). However, the study did not report the values for the higher-dose treatment group.[13] 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. In a double-Blind, Multicentre, randomized, parallel group study to assess the Efficacy and Safety of 400 mg of Velneperit (S-2367) and 120 mg of Orlistat Administered Individually or Combined Orally Three Times Per Day With a Reduced Calorie Diet (RCD) in Obese Subjects"results of this trial are same as of orlistst in relation to weight loss.[12] Shinogi has completed the phase II trials, and planning for phase III trials is under way.[13]

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. 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. 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. TransTech Pharma identified TTP435 as a potent and selective inhibitor of AgRP. 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: It is a methionine aminopeptidase 2 inhibitor. Originally developed as a treatment for solid tumors, it was initially thought to block angiogenesis and reduce adipose tissues by blocking blood supply. However, that administration of the drug caused profound weight loss in mice, which

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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 January 2011, Zafgen reported positive results from its phase Ib study using ZGN-433. A double-blind, placebo-controlled, multiple-ascending-dose study was performed in women with BMI 32–35kg/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. 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. Zafgen plans to initiate phase IIa studies in 2011.[11]

PP 1420: PP 1420 is a pancreatic polypeptide analogue. Previous studies of PP 1420 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.[12]

GSK 598809: GSK 598809 is a D_3 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. The medication is being developed for the treatment of substance dependence and other impulsive disorders. GlaxoSmithKline is currently completing phase I study designed to examine the behavioural and physiological effects of a single dose of GSK 598809 on food reward and reinforcement in relation to food-seeking behaviour under conditions of fasting, using neurocognitive and metabolic end points in subjects with obesity.

Ezlopitant: Ezlopitant is a neurokinin receptor-1 antagonist that has been implicated in both learned appetitive behaviours 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. 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.[16] Ezlopitant decreased intake of saccharin, but had no effect on water or salty solution consumption.

Thyroid hormone receptor agonists: Thyroid hormone affects different biological processes such as development, growth and metabolic control. Triiodothyronine (T3) is the biologically active form of thyroid hormone that acts through nuclear receptors, TR alpha and TR beta, regulating gene expression. The distribution of these receptors is heterogeneous amongst the different tissues, it is not surprising that some physiological effects of T3 are isoform specific. For example, while TRalpha is the dominant receptor in the brain and skeletal system and mediates most of the synergism between T3 and the sympathetic signaling pathway in the heart, TR beta is abundant in liver and is probably the isoform that mediates most of the T3 effects on lipid metabolism. Thus, it makes sense to develop compounds that selectively act on either one of the TRs, allowing for the activation of specific T3-dependent pathways. The available studies indicate that achieving selective activation of different TR-mediated pathways is a promising strategy for treating lipid disorders and obesity. GC-1, a selective TRβ agonist, when administered to rats, demonstrated a normalization of serum cholesterol and triglyceride levels. KB2115, a selective TRβ agonist, was administered to moderately

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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.[12]

11β-HSD1 inhibitor: The clinical trials involving patients with detailing compounds and strategies for selective 11β-HSD1 inhibition are available. Preclinical studies have shown proof of concept, with improved glucose tolerance and weight reduction reported in many diabetic and obese mouse models treated with 11β-HSD1 inhibitors.

PPAR Gamma: PPAR gamma plays a major role in differentiation of preadipocyte to adipocyte, the process of adipogenesis. Thus PPAR gamma agonists like pioglitazone enhance differentiation of adipocyte which caused weight gain in animals and humans. PPAR modulators are to develop agents that modulate PPAR gamma in such a way that the compounds improve insulin sensitivity without any promotion of weight gain. Another approach to try to overcome the increase in body weight seen with full PPAR gamma agonists is to develop agonists that act on two or all three of the PPARs, the hypothesis being that stimulating PPAR alpha and/or PPAR delta will activate fatty acid activation and cancel out the adipogenic effects of PPAR gamma agonism.[13]

PPAR-γ coactivator-1 α: Peroxisome proliferator-activated receptor-γ coactivator (PGC)-1α is a member of a family of transcription coactivator that plays a central role in the regulation of cellular energy metabolism. It is strongly induced by cold exposure, linking this environmental stimulus to adaptive thermogenesis. It participates in the regulation of both carbohydrate and lipid metabolism. It is highly likely that PGC-1α is intimately involved in disorders such as obesity, diabetes, and cardiomyopathy. Its regulatory function in lipid metabolism makes it an inviting target for pharmacological intervention in the treatment of obesity and Type 2 diabetes.[14] It is expressed at high levels in tissues where mitochondria are abundant and oxidative metabolism is active, such as brown adipose tissue (BAT), the heart, and skeletal muscle. Whereas the expression level is low in the liver and very low in white adipose tissue (WAT). PGC-1α also interacts with other nuclear hormone receptors such as PPAR-α, retinoic acid receptor, and thyroid receptor in BAT to enhance the expression of brown fat-specific uncoupling protein 1 (UCP1). UCP1 action leads to dissipation of the proton gradient and the uncoupling of oxidative phosphorylation, thereby increasing heat production.

Metformin Metformin is a biguanide that is approved for the treatment of diabetes mellitus, a disease that is exacerbated by obesity and weight gain. Metformin reduces hepatic glucose production, which is a major source of circulating glucose. Metformin also reduces intestinal absorption of glucose, which is a second source of circulating glucose. Finally, metformin increases the sensitivity to insulin, thus increasing peripheral glucose uptake and utilization. Metformin has been associated with significant weight loss when compared with sulfonylureas or placebo**.** Compared metformin and glipizide in a randomized double-blind study of Type II diabetic individuals who had failed on diet. The 24 subjects receiving metformin lost weight and had better diabetic control of fasting glucose and glycohemoglobin than did the glipizide group.[15] In a double-blind placebo-controlled trial in subjects with the insulin resistance syndrome, metformin also increased weight loss. Fontbonne et al.[12] Reported the results from the BIGPRO study, a 1-yr French multicenter study that compared metformin with placebo in 324 middle-aged subjects with upper body obesity and the insulin resistance syndrome.

The subjects on metformin lost significantly more weight (1–2 kg) than the placebo group. Although metformin may not give enough weight loss to receive an indication from the USFDA for treating obesity, it certainly deserves consideration in obese Type II diabetic individuals who have failed diet and exercise treatment for their diabetes, and it has been used in children.[16]

CONCLUSION: 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. 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. Given some of the molecular targets involved (e.g. monoamine transporters, CB1 receptors, 5-HT_{2C} receptors), such analyses should ideally include not only tests of feeding behavior but also, for example, tests relevant to mood, sexual behaviour, and learning and memory. However, even for those agents that meet preliminary requirements for selectivity of action and potential safety profile, extensive real-world testing is likely to be required by regulators, not only showing efficacy in terms of weight loss but also demonstrating long-term benefits for diabetes prevention and treatment, cardiovascular disease, and psychiatric safety. Finally, successful discovery and development of potent and safe drugs for the prevention and treatment of obesity will probably require polytherapeutic strategies as well as vastly improved tools for the identification and characterization of specific obese subpopulations that allow for the tailor-made development and appropriate use of personalized medicines.

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