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## NEW DRUG TARGETS TO TREAT THE OBESITY

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### ABSTRACT

**Background:** The incidence of obesity is increasing dramatically to epidemic proportions. There are few approved anti-obesity pharmacological treatments and their modest efficacy and safety concern. Presently two drugs approved by US FDA for treatment of obesity are Phentermine and Orlistat.

**Objective:** The aim of this review is to discuss the new pharmacological agents that are under development and that may be eventually used for treatment of obesity.

**Low doses of topiramate and phentermine:** The rationale 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 great efficacy.

**Bupropion and Naltrexone:** Monotherapy with bupropion shown weight loss of 2.8 kg at 52 weeks and this does not meet FDA criteria for an antiobesity drug. Naltrexone alone is associated with minimal weight loss. Combination would be associated with weight reduction.

**Zonisamide and Bupropion:** Zonisamide induces weight loss as a side effect. 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.

**Liraglutide:** Victoza (liraglutide) is a once-daily version of the new-generation GLP-1 (glucagon like peptide) analogs. Victoza reduces body weight and body fat mass through mechanisms involving reduced hunger and lowered energy intake.

**Cetilistat:** 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. Phase III trials of cetilistat are currently under way in Japan.

**TTP 435:** TTP435 is a potent and selective inhibitor of AgRP. TTP435 was shown to reduce food intake and body weight gain, reduce fat composition, and reduce insulin levels in a dose-dependent fashion.

**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.

**Conclusion:** Many factors have mitigated against active drug development, including the poor safety and efficacy of previous antiobesity drugs. The new generation of antiobesity drugs offers hope for the management of obesity, although no single agent is likely to be a solution.

**Keywords-** phentermine, fenfluramine, orlistat, obesity

### INTRODUCTION

The incidence of obesity is increasing dramatically to epidemic proportions in almost

all societies of the world and with it come the major pathological complications including hypertension, type 2 diabetes.<sup>1</sup> DM,

osteoarthritis, dyslipidemia, obstructive sleep apnoea and some cancers.<sup>2</sup>

Many of these diseases can be prevented or ameliorated with a reduction in body weight. Despite dramatic advances in our understanding of central regulation of energy balance and obesity, there are few approved antiobesity pharmacological treatments and their modest efficacy and safety concern.<sup>3</sup>

### Regulatory authorities

**European Union:** a mean weight loss of 10% from the baseline after 1 year of treatment.

**US FDA :** >5 % placebo subtracted weight loss difference after 1 year.<sup>4</sup>

Obesity is a fetal chronic relapsing disease, the most prevalent of 21<sup>st</sup> century .Despite rigorous attempts at behavioural 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.<sup>5</sup>

So there is need of continuous dialogue between obesity researchers, pharmaceutical industries and regulatory authorities to stimulates research and drug development based on the clinical need of the patients and recognising the true clinical endpoints should be the priority to allow appropriate risk: benefit assessment.<sup>6</sup> There are two drugs approved by US FDA for treatment of obesity<sup>7,3</sup>.

**Phentermine**, approved in 1959, is the most commonly prescribed antiobesity agent in the United States.

**Orlistat**, approved in 1999, is an oral lipase inhibitor that reduces absorption of dietary fat.

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.<sup>7</sup>

**Limitations: valvulopathy:** fenfluramine and dexfenfluramine,

**Abuse potential and psychiatric side effects:** rimonabant,

**Cardiac adverse events:** sibutramine.<sup>8</sup>

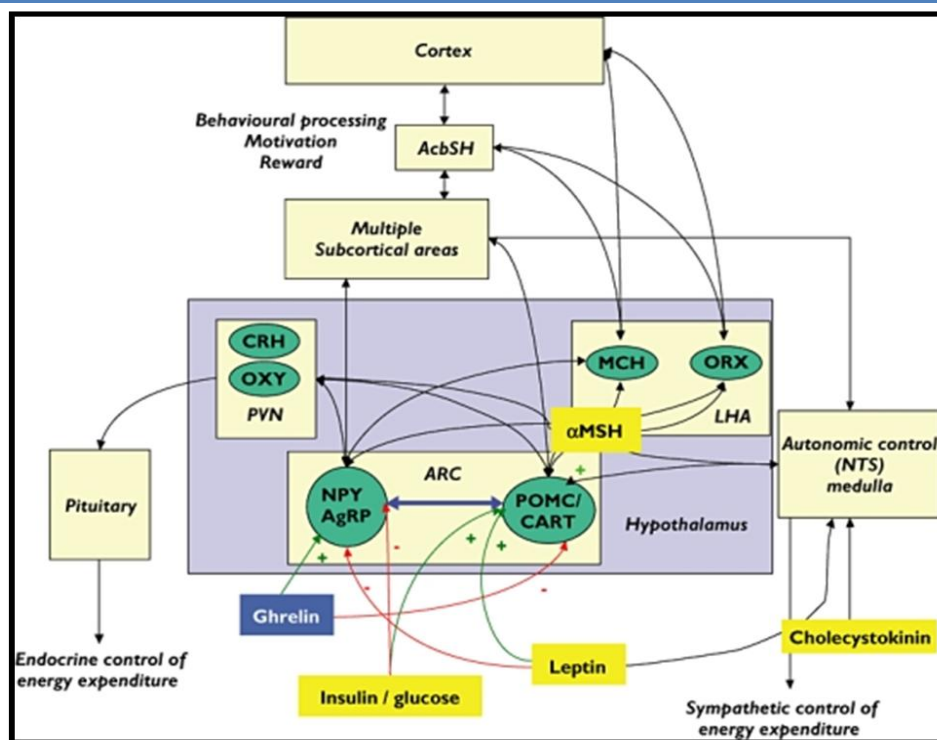
### HISTORY OF ANTI OBESITY MEDICINE

Drugs	FDA approval date	FDA withdrawal date
Phentermine	5/1959	Still in use
Fenfluramine	6/1973	9/1997
Dexfluramine	4/1996	9/1997
Orlistat	4/1999	Still in use
sibutramine	11/1997	10/2010
Rimonabant	6/2006	10/2008

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

### 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



Circuits implicated in the central control of feeding. AcbSH, nucleus accumbens shell; AgRP, agouti gene-related peptide; ARC, arcuate nucleus; CART, cocaine-amphetamine regulated transcript; CCK, cholecystokinin; CRH, corticotrophin releasing hormone; LHA, lateral hypothalamus;  $\alpha$ -MSH, alpha-melanocyte stimulating hormone; MCH, melanin-concentrating hormone; MC4R, melanocortin 4 receptor; NPY, neuropeptide Y; NTS, tractus solitarius; ORX-orexin (hypocretin); OXY, oxytocin; POMC, pro-opiomelanocortin; PVN, periventricular nucleus.

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  $\alpha$ -melanocyte-stimulating hormone ( $\alpha$ -MSH) release and decreasing

MCH/ORX activity, leading to satiation and a termination of feeding.<sup>6</sup>

### Combination Therapy

#### Low doses of topiramate and phentermine (Qnexa):

Phentermine, an amphetamine derivative, has been on the market for more than 30 years for short-term treatment of obesity.

Topiramate has been approved for migraine prophylaxis and the treatment of seizure disorders. Early 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  $\text{A}$  receptors which causes inactivation of Na channels. The modulation of  $\gamma$ -amino butyric acid may have a role in the reduction of food intake.<sup>9</sup>

The rationale 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 great efficacy.

In oct.2010 ,the FDA did not approved QNEXA because of the elevated heart rate associated with its use , teratogenic potential of drug .In Jan. 2011 VIVUS announced that FDA had

requested additional information regarding teratogenicity and company will continue to work with FDA in an effort to secure approval.

VIVUS has completed three Phase III studies of Quinexa. Results of this trial are given in the table.

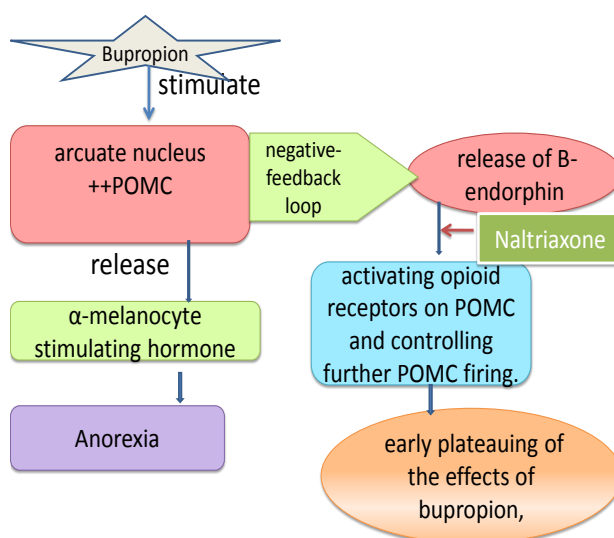
VIVUS PHASE III TRIALS of <i>Qnexa</i>			
	EQUATE	EQUIP	CONQUER
Duration (Wks)	28	56	56
BMI (kg/m <sup>2</sup> )	30-45	>42.5	>36.3
End points (Wt.loss)	>5%	>5%	>5%
No.of pts	756	1267	2487
Dropout rate		31%	41,31,36%

### Bupropion and Naltrexone (Contrave)

A dual antiobesity agent .It is combination of bupropion and naltrexone. Bupropion 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.<sup>10</sup> As monotherapy naltrexone is associated with minimal weight loss.<sup>3</sup>

Thus combining these two agents would associate with clinically meaningful and sustained pattern of weight reduction.



In a double-blind placebo-controlled study, enrolling 419 obese subjects BMI 30–40 kg/m<sup>2</sup> over a period of 24 weeks. The subjects were receiving one of the following:

Placebo, Naltrexone 48 mg alone, Bupropion slow-release (SR) 400 mg alone, or combinations of Bupropion 400 mg with varying doses of Naltrexone (16 mg, 32 mg, and 48 mg).<sup>11</sup>

At 24 weeks, the average weight loss in each of the groups was as, 0.9 kg 1.1 kg; 2.6 kg; for alone drug and

With (400 mg Bupropion) + (Naltrexone 16 mg, 32mg, 48mg, ) 5.1 kg; 5.1 kg, and 4kg respectively.

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 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.

### **Zonisamide and Bupropion (Empatic)**

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.

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.<sup>12</sup> 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.<sup>7</sup>

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 27–45 kg/m<sup>2</sup>.

The patients were randomized to one of six arms: Two groups: 1) Bupropion IR 360 mg + Zonisamide SR 120 mg 2) Bupropion IR 360 mg + Zonisamide SR 360 mg,

Three single-treatment groups 1) Bupropion IR 360 mg, 2) Zonisamide SR 360 mg, 3) Zonisamide SR 120 mg and 4) Placebo.

The combination therapy containing zonisamide 120 mg, 360mg given weight loss of 6.1% and 7.5%. 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 leads to massive obesity. At first here was hope that leptin would be a successful treatment option to combat obesity. 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.<sup>2</sup>

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.<sup>13</sup>

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 the presence of amylin may

“prime” the hypothalamus to respond better to leptin.

In a 28-week, double-blind, placebo-controlled study enrolled 608 obese BMI 27–45 kg/m<sup>2</sup>. After a 1-week placebo lead-in period, the subjects were randomized to twice-daily therapy with 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. 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.

### Monotherapy in Phase II/III Trials

**Lorcaserin** Lorcaserin is a 5HT-2C receptor agonist. Fenfluramine, a previously marketed non selective 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<sup>14</sup> where as 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; therefore become a target of interest.

DM patients who were overweight or obese. (N=604)

Drugs	Wt.Loss (12Wks)	Valvulopathy (24Wks)	Valvulopathy (52Wks)
Lorcaserin 10 mg BD	4.5%	2.5%	2.9%
lorcaserin 10 mg OD	2.5%	2.5%	2.5%
placebo.	1.5%	1.9%	0.5%

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.

**Liraglutide:** GLP-1 is a humoral gut peptide that improves 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 (1.2, 1.8, 2.4 or 3.0 mg, 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.<sup>15</sup>

Mean weight loss with liraglutide was 4.8 , 5.5 , 6.3 , and 7.2 kg respectively as compared with 2.8 kg and 4.1 kg with placebo and orlistat. Nausea and vomiting more in liraglutide than in placebo, but mainly transient and rarely led to discontinuation of treatment.

"This is 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 (liraglutide) 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.

**Semaglutide**, a **once-weekly** GLP-1 analogue, Semaglutide, is based on a different molecule than Victoza, has finished phase II trials.

Taspoglutide, under development by Roche Holding AG and Ipsen SA, is another GLP-1 drug for type-2 diabetes.<sup>16</sup>

Novo Nordisk remains committed to the development of a longer-acting GLP-1 analogue. 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.

**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.<sup>17</sup>

**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 in 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<sup>2</sup>. 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. There was a notable dose-dependent increase in heart rate up to 8.5 beats per minute 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.<sup>18</sup>

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.

Neuro Search has decided that a phase 3 program including two obesity studies of one year each is the best way to proceed. This phase 3 program must also include a study for more than a two year period in order to determine the drug's cardiovascular safety profile.

**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.

**RCT study: BMI 30–45 kg/m<sup>2</sup> (N=656)**

Reduced-calorie diet regimen(800 kcal/day) to all subjects for 6-week				
Drugs	Diet	Duration	Weight Reduction(kg)	Adverse Effects
Velneperit 800 mg OD	800 kcal/day	54 weeks.	3.8	Nasopharyngitis, URTI, Sinusitis, headache. Mild decreases in Hematocrit, Hb%, RBCs ,
Velneperit 1,600 mg OD		54 weeks.	not reported	
Placebo		54 weeks.	0.8	

In a double-blind, multi-center, 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 orlistat in relation to weight loss.<sup>20</sup>

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

**Obinepitide:** Obinepitide is a synthetic analogue 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 and Y1 receptor is associated with cardiovascular side effects.

In March 2006, 7TM Pharmaceutical 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 hrs. after drug administration relative to placebo. Obinepitide is under development.

**Early-Phase Drugs (Phase I)**

**TTP 435:** 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 Pharmaceutical 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:** ZGN-433 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 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 32–35 kg/m<sup>2</sup>, with 24 subjects enrolled in the core study.

Primary objective: to evaluate the safety and tolerability of the compound.

Second objective: 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. In addition, there was a decline in hunger, 38% reduction in triglyceride levels, and 23% reduction in LDL cholesterol. Zafgen plans to initiate phase IIa studies in 2011.<sup>21</sup>

**PP 1420:** PP 1420 is a pancreatic polypeptide analog that is thought to increase satiety. Previous studies of PP1420 have shown that injections of human PP have the effect of reducing appetite and food intake. Human PP has a 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.<sup>22</sup>

**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 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. The study was scheduled to be completed in mid-2011; no further data have been released.

**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. Further studies have yet to be done.<sup>23</sup>

To evaluate the selectivity of the NK1-receptor antagonist in decreasing consumption of sweetened solutions, they compared the effects of ezlopitant on water, saccharin-, and sodium chloride (NaCl) solution consumption. Ezlopitant decreased intake of saccharin, but had no effect on water or salty solution consumption.

#### **Thyroid hormone receptor agonists**

Thyroid hormone affects in a myriad of biological processes such as development, growth, and metabolic control. Triiodothyronine (T<sub>3</sub>) 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 T<sub>3</sub> are isoform specific. For example, while TR $\alpha$  is the dominant receptor in the brain and skeletal system and mediates most of the synergism between T<sub>3</sub> and the sympathetic signaling pathway in the heart, TR $\beta$  is abundant in liver and is probably the isoform that mediates most of the T<sub>3</sub> 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 T<sub>3</sub>-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 TR $\beta$  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. The accelerated metabolic rate was followed by a decrease in fat but not in lean mass. In other studies, KB2115, a selective TR $\beta$  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 TR $\beta$  receptor agonists in treating dyslipidemia, but they may become a potential target for antiobesity treatment soon<sup>24</sup>

**11 $\beta$ -HSD1 inhibitor:** 11 $\beta$ -HSD1 is a bidirectional enzyme that interconverts hormonally inactive cortisone to cortisol. Preclinical animal studies have shown proof of concept, with improved glucose tolerance and weight reduction reported in many diabetic and obese mouse models treated with 11 $\beta$ -HSD1 inhibitors. Phase I and II clinical data reported at the American Diabetes Association's Scientific Sessions in June 2008 were equally encouraging.<sup>25</sup>

**PPAR gamma ( $\gamma$ ):** 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 stimulating PPAR  $\delta$ , PPAR  $\gamma$  will activate fatty acid activation and

cancel out the adipogenic effects of PPAR  $\gamma$  agonism.<sup>26</sup>

**PPAR- $\gamma$  coactivator-1  $\alpha$ :** Peroxisome proliferator-activated receptor- $\gamma$  coactivator (PGC)-1 $\alpha$  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-1 $\alpha$  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.<sup>27</sup>

PGC-1 $\alpha$  also interacts with other nuclear hormone receptors such as PPAR- $\alpha$ , 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. Although, the cellular mechanism for the effects of metformin are poorly understood.

It has three effects at the clinical level---

- 1) It reduces hepatic glucose production, which is a major source of circulating glucose.
- 2) It reduces intestinal absorption of glucose, which is a second source of circulating glucose.
- 3) It increases the sensitivity to insulin, thus increasing peripheral glucose uptake and utilization.

Metformin has been associated with significant weight loss when compared to sulfonylureas or placebo.

Campbell et al. compared metformin and glipizide (Mylan, Morgantown, WV) 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.<sup>28</sup> In a double-blind placebo-controlled trial in subjects with the insulin resistance syndrome, metformin also increased weight loss. Fontbonne *et al.* 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.<sup>29</sup>

## 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.

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