Pharmacology, Biochemistry and Behavior 97 (2010) 63–83

Contents lists available at ScienceDirect

Pharmacology, Biochemistry and Behavior

journal homepage: www.elsevier.com/locate/pharmbiochembeh

Review

New approaches to the pharmacological treatment of obesity: Can they break through the efficacy barrier?

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ARTICLE INFO

Available online 3 August 2010

Keywords:
Anorectic
Obesity
Anti-obesity drug

ABSTRACT

In this review we assess the range of centrally active anorectics that are either in human clinical trials, or are likely to be so in the near future. We describe their weight loss efficacy, mode of action at both pharmacological and behavioural levels, where understood, together with the range of side effects that might be expected in clinical use. We have however evaluated these compounds against the considerably more rigorous criteria that are now being used by the Federal Drugs Agency and European Medicines Agency to decide approvals and market withdrawals. Several trends are evident. Recent advances in the understanding of energy balance control have resulted in the exploitation of a number of new targets, some of which have yielded promising data in clinical trials for weight loss. A second major trend is derived from the hypothesis that improved weight loss efficacy over current therapy is most likely to emerge from treatments targeting multiple mechanisms of energy balance control. This reasoning has led to the development of a number of new treatments for obesity where multiple mechanisms are targeted, either by a single molecule, such as tesofensine, or through drug combinations such as qnexa, contrave, empatic, and pramlintide + metreleptin. Many of these approaches also utilise advances in formulation technology to widen safety margins. Finally, the practicality of peptide therapies for obesity has become better validated in recent studies and this may allow more rapid exploitation of novel targets, rather than awaiting the development of orally available small molecules. We conclude that novel, more efficacious and better tolerated treatments for obesity may become available in the near future.

Contents

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doi:10.1016/j.pbb.2010.07.020

1. Introduction

Obesity is a chronic state associated with a wide range of metabolic and cardiovascular conditions such as dyslipidaemia, atherosclerosis, hypertension and type 2 diabetes which also substantially increase the risk of stroke, angina and myocardial infarction. Obesity also predisposes to colon, breast, kidney and digestive tract cancers. In addition, non-life threatening disease states associated with obesity include arthritis, sleep apnea, gallstones and gout as well as low self esteem and affective disorder (Heal et al., 2009). There is also growing evidence that obesity and type II diabetes may predispose towards Alzheimer's disease (Luchsinger and Gustafson, 2009). Unfortunately, the increasing adoption of Western diet and sedentary lifestyle throughout the world is causing a global increase in obesity and, unless checked, is expected to become an indirect but leading cause of mortality and morbidity (Heal et al., 2009). Diet and exercise are the most obvious remedies for obesity but have proved ineffective for most individuals (e.g. Wu et al., 2009). Pharmaceutical companies have therefore sought to discover novel therapies that could serve as adjunctive treatments in support of diet, exercise and lifestyle modification regimes (Table 1).

To this end, a number of treatments have been introduced for the treatment of obesity. The most widely used at present are phentermine, sibutramine and orlistat. All three are associated with between 3 and 5% body weight loss over 6–12 months (see Table 2) in addition to that achieved by placebo controls (Li et al., 2005). Efficacy of this magnitude seems undeniably modest, but is only just below the criterion of 5–10% weight loss that is associated with clinically meaningful reductions in the risk of obesity co-morbidities (Goldstein 1992, Knowler et al., 2002). One of the principal reasons that all three of these most commonly prescribed agents fail to exert greater efficacy is the need to limit dosage to avoid significant tolerability issues. Indeed, the most efficacious of the three, sibutramine, can no longer be prescribed in Europe due to concerns of increased risk of heart attacks and strokes (See Section 7.9). The use of phentermine is also limited by the risk of cardiovascular effects and abuse potential (See Section 7.7) and it is not available for use in Europe. In contrast to both sibutramine and phentermine, orlistat, a gut lipase inhibitor, is not associated with major safety concerns. Indeed, the drug is itself not absorbed from the gut. However, by preventing the breakdown of ingested fats in the gut and thereby preventing their absorption, orlistat causes socially undesirable side effects such as oily stools, faecal spotting and faecal urgency, diarrhoea, flatulence, dyspepsia and gastric pain (Li et al., 2005; Filippatos et al., 2008). Orlistat also interferes with the absorption of many drugs and fat soluble vitamins, the latter giving concerns over the effects of long term use (Filippatos et al., 2008).

For these reasons, new treatments for obesity that are better tolerated and more efficacious are urgently needed.

2. Metabolic syndrome

Metabolic syndrome is a clustering of specific cardiovascular disease risk factors whose underlying pathophysiology is thought to be related to insulin resistance. The amelioration of these symptoms is considered key to reducing mortality associated with obesity co-morbidities. The key measure of efficacy taken in the present review is the degree of weight loss as opposed to a wider measure based on components of the metabolic syndrome. Weight loss in obese subjects leads to predictable improvements in a number of metabolic parameters such as insulin

Table 1
Promising centrally acting treatments for obesity.

Treatment (Developer)	Components	Mechanism of action		Clinical trial phase
		Pharmacological	Pharmacokinetic	
Lorcaserin (Arena)		5-HT_{2C} agonist		III
Tesofensine (NeuroSearch)		NA/5-HT/DA reuptake inhibitor		III
Contrave(Orexigen)	Naltrexone + bupropion	Opiate antagonist + NA/DA reuptake inhibitor	Delayed release formulation	III
Empatic (Orexigen)	Zonisamide + bupropion	Anticonvulsant + DA/NA reuptake inhibitor	Delayed release formulation	II
Qnexa (Vivus)	Phentermine + topiramate	NA/DA releasing agent + anticonvulsant	Controlled release topiramate	III
Metreleptin/Pramlintide (Amylin)		Leptin analogue + amylin analogue	Leptin + long acting amylin analogue	II

Table 2
Efficacy of current pharmacological treatments for obesity (from meta-analysis of ITT LOCF clinical trial results by Li et al., 2005).

Treatment	Dose	Diet restriction and behavioural modification	Trial duration (weeks)	Placebo-adjusted Wt loss kg (%)
Sibutramine	10–20 mg	Yes	52	4.5 kg (4.5%)[a]
Orlistat	360 mg	Yes	52	2.8 kg (2.8%)[a]
Phentermine	15–30 mg	Yes	2–24	3.6 kg (3.6%)[a]
Diethylpropion	75 mg	Yes	6–52	3.0 kg (3.0%)[a]
Bupropion	300–400 mg	Yes	24–52	2.8 kg (2.8%)[a]
Topiramate	96–196 mg	Yes	24	6.6 kg[a] (6.5%)

[a] These values were not reported in the meta-analysis of Liu et al (2005) but have been estimated by assuming a mean starting body weight of 99.5 kg (the mean value of studies reviewed in Table 3).

resistance, hyperinsulaemia, hyperglycaemia, lipid profile, and hypertension. In addition some drugs may have additional beneficial actions in relation to one or more of these parameters. However, we have not reviewed activity against these parameters for two reasons. Firstly, many of the studies reviewed have either not consistently measured or have yet to report metabolic parameters. A second reason for not addressing metabolic syndrome is the current lack of consensus as to its definition and the interpretation of changes in individual components (Kahn, 2007; Heal et al., 2009).

3. Criteria for regulatory approval of treatments for obesity

The criteria set by the Food and Drug Administration (FDA) for development of drugs for obesity have recently been revised (FDA, 2007) and now require either ≥5% statistically significant, placebo-adjusted weight loss after 1 years treatment or that >35% of patients achieve >5% weight loss and this is approximately double the proportion and significantly different from the placebo-treated group. Evidence for improvements in co-morbidities such as lipids, glycaemia or blood pressure is also required. Guidelines for approval in Europe have also been revised by the European Medicines Agency (EMA) and seek ≥10% weight loss from baseline over 1 year which should also be >5% above that achieved by placebo (EMA, 2007). This weight loss should be maintained after treatment ceases and EMA cites prevention of weight gain as an important secondary endpoint, although this has yet to be demonstrated for any current anti-obesity treatment. In addition, EMA require improvements in lipids, glycaemia, blood pressure, cardiac function, waist circumference, waist–hip ratio, ultrasensitive C-reactive protein, a marker of low level inflammation associated with obesity (Visser et al. 1999), sleep apneas and quality of life measures as secondary endpoints. The emphasis that both the FDA and EMA have placed on metabolic indices is based on the recognition that they more directly impact on the onset of cardiovascular disease and mortality than weight loss alone. Treatments that reduce weight, but do not affect cardiometabolic risk would be considered of cosmetic benefit only and would thereby be less likely to gain approval for clinical use.

Anti-obesity drugs have generated a number of safety issues in the past, such as the development of valvulopathy after treatment with fenfluramine particularly when combined with phentermine (Connolly et al., 1997), primary pulmonary hypertension (PPH) in those treated with fenfluramine and dexfenfluramine (Abenheim et al., 1996), abuse potential of amphetamine-like compounds (Craddock, 1976), increased blood pressure in those treated with agents acting by enhancing catecholaminergic mechanisms such as sibutramine (Hansen et al., 1999; Kim et al., 2003) and more recently, psychiatric effects associated with the cannabinoid CB_1 receptor antagonist, rimonabant (Christensen et al., 2007). As obesity is not itself a disease, poses no immediate threat to life and can be addressed without risk by diet, exercise and lifestyle changes, albeit ineffectually for most in the long term (Wu et al., 2009), a high degree of safety is required of anti-obesity treatments. The FDA therefore requires that weight loss be predominantly from fat, while both the FDA and EMA focus on the liability for abuse, psychiatric side effects and the effects of withdrawal for centrally acting agents. Cardiovascular safety is also stressed as the obese population already has compromised cardiovascular function. These guidelines clearly set high hurdles for any prospective treatment to overcome. The experience with rimonabant, sibutramine and possibly qnexa suggests that regulatory bodies are increasingly reluctant to approve drugs without data that unambiguously supports long term safety. This follows recognition that the beneficial effects of all current weight loss treatments are reversed on withdrawal, implying that repeated courses of treatment would be required to maintain any health benefits gained.

4. Peptide targets and their receptors

4.1. Gut-related peptide families

Gut peptides and their receptors represent a potentially attractive route to reducing food intake, and hence body weight, in the context of the treatment of obesity. However these peptides are expressed in multiple body systems in addition to the organs of the gut, and may have functions that are unrelated to the control of energy balance. Although these peptides are important signals of gut nutrient status to the brain, they also have roles in the modulation of peripheral physiology, such as the metabolism and storage of the products of digestion. In addition to signalling nutrient status, they may also provide information to the brain about aversive gut states, such as excessive stomach volume and the presence of toxins. These different roles inevitably complicate their possible utility in the treatment of obesity.

About 1% of the cells lining the lumen of the intestine have an entero-endocrine function (Schonhoff et al., 2004). They differentiate into at least 15 subtypes, distinguished by their particular endocrine products. The peptides themselves fall naturally into several classes according to the precursor protein from which they are cleaved.

Cholecystokinin (CCK) derives from procholecystokinin which is closely related to progastrin, that gives rise to gastrin. The cellular processing of procholecystokinin gives rise to a series of fragments of different length, including CCK-8, CCK-39 and CCK-58, in a tissue dependent manner (Miller and Gao, 2008). CCK and gastrin act at two closely related G-protein receptors, CCK-1 and CCK-2 (formerly known as CCK-A and CCK-B). Both receptor subtypes are widely distributed in both gut and brain, with the CCK-2 receptor having a particularly broad localisation in cortex and striatum as well as in the hindbrain. Gastrin binds with low affinity to the CCK-1 receptor, but both peptides are active at the CCK-2 receptor (Miller and Gao, 2008).

Proglucagon contains, in addition to the amino acid sequence for glucagon, the sequences for GLP-1 (Tomas and Habener, 2009) and for glicentin, which in turn gives oxyntomodulin. Glucagon acts primarily at the glucagon receptor, GLP-1 at the GLP-1 receptor and oxyntomodulin at both. It has been suggested that there may be an additional undiscovered GLP-1 receptor subtype in the periphery (Tomas and Habener, 2009).

The NPY family contains three members (neuropeptide Y—NPY; pancreatic polypeptide—PP; and peptide tyrosine tyrosine—PYY), which are expressed by activation of separate, but related, genes. NPY is expressed in many brain areas and associated with modulation of learning and memory and a variety of other functions, in addition to its well known orexigenic action. PPY is released by the L cells lining the gut and mostly circulates as PYY_{3-36}. PP originates from the Islets of Langerhans in the pancreas where it has an important role in regulating pancreatic secretion. The peptides of this family act at multiple receptors known as Y_1, Y_2, Y_4, Y_5 and Y_6 (Lindner et al., 2008). Three of the receptor subtypes (Y_1, Y_4 and Y_6) are members of a related receptor family sharing about half their amino acid sequence, but the remaining two receptor subtypes are unrelated to this group

or to each other. PP is a potent agonist at the Y_4 receptor. NPY and PYY have high affinity for the Y_1 and Y_4 receptors. Expression of the Y_5 receptor is confined to the CNS and NPY is a potent ligand. The Y_6 receptor is relatively little studied at present.

Ghrelin was discovered following the characterisation of a receptor whose activation promoted the release of growth hormone, the growth hormone secretagogue receptor (GHS-R). The endogenous ligand, ghrelin, was identified subsequently and shown to have a powerful orexigenic effect. Ghrelin is cleaved from preproghrelin as 27 and 28 amino acid peptides and is highly conserved in mammals (Castañeda et al., 2009). Another product of preproghrelin is obestatin, which has the opposite effect to ghrelin on food intake and body weight (Zhang et al., 2005).

4.2. Non-gut peptide targets

In addition to these gut peptide families and their receptors, there are a number of other peptide targets that have attracted interest in the last two decades. They include amylin, leptin, melanin concentrating hormone (MCH) and α-melanocyte stimulating hormone (αMSH).

Amylin is a 37 amino acid peptide that is synthesised in the cells of the pancreas and co-released with insulin. It is a member of the calcitonin peptide family and has a complex receptor pharmacology. There are three known receptors, (AMY_1, AMY_2 and AMY_3), which are heteromers of the calcitonin calcitonin-like receptor and different receptor-activity-modifying proteins (Qi et al., 2008). Amylin receptors are widely distributed in the rhesus brain, including area postrema, hypothalamic nuclei and the nucleus accumbens (Paxinos et al., 2004).

Leptin is a cytokine that was originally characterised as a product of adipocytes although it is now clear that it is synthesised very much more widely, both peripherally and in the brain (Ahima and Flier, 2000). There is a single known receptor, but with multiple isoforms, which is expressed both peripherally and centrally. The long form isoform, LRb, mediates the cellular actions of leptin.

MCH is a 17 amino acid peptide with a cyclic structure. It was first detected in teleost fish where it modulates the distribution of melanin within melanosomes, leading to a darkening or lightening of skin colour (Pissios et al. 2006). It is expressed in the hypothalamus and was subsequently detected in other vertebrates including mammals. A role in feeding and energy balance is suggested by the hypothalamic expression pattern and the stimulation of feeding following intracerebroventricular administration. MCH KO mice are lean and hypophagic (Shimada et al 1998) and mice with selective loss of MCH expressing hypothalamic cells show a similar phenotype of late developing leanness (Alon and Friedman 2006). There are two MCH receptors (MCHR1 and MCHR2) with similar expression patterns but limited homology. MCHR1 is the more widely expressed in primates and is the only receptor to have been detected in rodents (Pissios et al., 2006).

αMSH is a 14 amino acid peptide derived from proopiomelanocortin (POMC). POMC also contains the peptide sequences for the opioid peptide β-endorphin and for ACTH as well two other variants of MSH and is widely expressed in brain and other tissues. αMSH acts through five separate melanocortin receptors (MC1R, MC2R, ..., MC5R). There is substantial evidence to link the actions of αMSH at the MC4R with feeding and body weight regulation (Cone 2005). MC4R's are expressed in brain areas, particularly the arcuate nucleus of the hypothalamus and hindbrain, associated with the regulation of feeding and MC4R KO mice have a pronounced obesity phenotype (Adan et al. 2006). In addition, loss of function mutations in MC4R is associated with severe human obesity and excess energy intake; body mass index (BMI) correlates inversely with the degree of loss of function (Farooqi et al., 2003). There is also some evidence to suggest that the MC3R is involved in energy balance and body weight (Cone 2005).

5. Peptide targets in the treatment of obesity

5.1. Cholecystokinin

The first gut peptide to be unambiguously identified as having a role enhancing the satiety response to ingested foods was chloecystokinin (Woods, 2004). Smith and Gibbs (1992) originally concluded that the actions of CCK met a series of criteria including (i) release correlated with ingestion of food, (ii) an action that reduced feeding behaviour while preserving the natural behavioural satiety sequence and (iii) a hyperphagic action of CCK antagonists. These criteria remain important in characterising the effects of other gut peptides on feeding behaviour. The mechanism of action in relation to feeding has been clearly established. Cholecystokinin is released from the proximal part of the duodenum in response to presence of digestion products and reaches peak levels within 30 min of a meal and then declines over a period of several hours (Moran and Kinzig, 2004). The hormone stimulates the release of bile from the gall bladder and also stimulates vagal afferent projecting to hindbrain nuclei, such as the nucleus of the solitary tract. It also sensitises vagal afferents that are stimulated by increased stomach volume. At a behavioural level, the effects of CCK are recognised as a reduction in meal size rather than meal frequency and by a leftward shift in the satiety sequence. Both findings are consistent with enhancement of satiety by CCK. Studies using selective agonists and antagonists suggest that the effect of CCK depends on stimulation of CCK-1 receptors and requires that the vagus nerve is intact (Moran and Kinzig, 2004). Taken together, these findings suggested that CCK itself is an important signal of gut function to the brain and that CCK agonists might be useful in the treatment of obesity.

A recent study in humans demonstrated that the orally active CCK-1 agonist GI181771X was able to slow gastric emptying without inducing gastrointestinal side effects in most participants in the study. A subsequent Phase III study randomised more than 700 obese individuals (BMI $\geq$30 or $\geq$27, with additional risk factors) to a 27 week double-blind study. No gall bladder- or pancreas-associated side effects were detected although gastrointestinal side effects were more common in the treatment group. There was no significant effect of treatment on either body weight or waist circumference, though aspects of the study design have been questioned (Roses 2009). Other groups, including Merck, are also developing orally active CCK-1 agonists. Although the CCK-2 receptor has generally been discounted as a target for obesity treatment, it has recently been reported that the mice with non-functional CCK-2 receptors have an obese phenotype (Clerc et al., 2007), so it is possible that this receptor may provide an additional therapeutic route to the treatment of unwanted weight gain.

5.2. Glucagon-like peptide 1 (GLP-1) and oxyntomodulin

GLP-1, and the related hormone GIP (originally known as 'gastric inhibitory hormone', but now referred to as 'glucose-dependent insulinotropic peptide'), are examples of *incretins*—neural or humoral factors that enhance insulin secretion. Although there is little evidence to suggest that GIP is involved in body weight control, GLP-1 is of considerable interest. Rodent studies initially identified a reduction in food intake following administration of GLP-1 (Tang-Christensen et al., 1996; Turton et al., 1996) and subsequently a similar effect was identified in humans with Type-2 diabetes following infusion with GLP-1 (Gutzwiller et al., 1999). A study in rhesus monkeys demonstrated that the reduction in feeding was associated with a reduction meal size rather than in meal frequency. GLP-1 receptors are located in relevant peripheral and central sites to achieve this effect. For example, they are expressed on vagal afferents projecting to the hindbrain and also in relevant hypothalamic and other forebrain nuclei. In addition to the role of GLP-1 receptors in modulating feeding, they are also implicated in the development of

conditioned taste aversions. Studies in rodents suggest these two roles are anatomically separated, with GLP-1 receptors in the central nucleus of the amygdala supporting the development of taste aversion and other populations, presumably hypothalamic or hindbrain, being involved in reduced food intake (Kinzig et al., 2002). The release of GLP-1, like that of insulin and ghrelin, can be stimulated by conditioned cues in advance of feeding (Vahl et al., 2010). This suggests that it has an important role in preparing the body for the short term homeostatic disturbance that arises from eating food. Thus, in addition to promoting the development of satiety to ingested food, GLP-1 may also mediate anticipatory physiological responses to the onset of feeding.

GLP-1 is degraded by diaminopeptidyl peptidase-4 (Dpp4), to GLP-1 (7–36) amide, which is only a weak agonist at the GLP-1 receptor (Tomas and Habener, 2009). However a number of modified peptides have been shown to resist degradation by this enzyme. These include exenatide (Byetta, Eli Lilly) and liraglutide (Novo-Nordisk). In clinical use exenatide is administered twice a day, before meals, by sc injection. In combination with a drug such as metformin, glycaemic control is improved. In the final phase of one clinical trial (DeFronzo et al., 2005), the effects of twice daily 5 μg or 10 μg exenatide were compared with placebo. Exenatide, in addition to lowering glycated haemoglobin (HbA_{1C}), reflecting improved glycaemic control, led to a dose-related reduction in body weight at 30 weeks (placebo: 0.3 kg; 5 μg: 1.6 kg; 10 μg: 2.8 kg). The reduction in body weight was most rapid at the beginning of the treatment period, when GI side effects, including nausea, were also at a maximum. However, at the individual level, there was no relationship between the degree of reported nausea, and the extent of body weight reduction. The authors therefore argued that the reduction in body weight was not due to loss of appetite through nausea. Whilst the degree of weight loss associated with exenatide may be insufficient to achieve the >5% baseline adjusted weight loss required for regulatory approval as a weight loss agent, it is a welcome feature in a drug licensed for the treatment of type II diabetes, many of which cause no weight loss or even weight gain (e.g. PPARγ agonists).

Recent data has suggested that combined GLP-1 and glucagon receptor agonism may have superior efficacy in inducing reduced food intake and body weight reduction. Such a hypothesis is plausible because administration of sub-chronic doses of glucagon is known to reduce food intake and body weight in rodents. Day et al (2009) synthesised chimerae of GLP-1 and glucagon and went on to show that these molecules had *in vitro* action at both receptors. Subsequent *in vivo* studies used diet-induced obese mice. In a one week study of an Aib2 C24 chimera 2 lactam with balanced efficacy at the two receptors, both body weight and food intake were decreased. A subsequent study lasting one month also revealed decreased body weight associated with an increase in energy expenditure that did not reflect changes in spontaneous activity. This pattern of initially reduced food intake and a subsequent maintenance of reduced body weight is similar to that obtained in many other studies of anorectic agents, but the documented increase in energy expenditure suggests a potentially valuable clinical gain. A similar conclusion in relation to energy expenditure was reached by a second group (Pocai et al., 2009) pursuing the same therapeutic approach.

Oxyntomodulin, secreted by L cells lining the gut, is released during ingestion of food. It is known to delay gastric emptying and to reduce gastric acid secretion. It also reduces feeding in the rat, an action which is blocked following co-administration of a GLP-1 antagonist (Dakin et al., 2001). Two studies in obese humans have suggested that oxyntomodulin, or related peptides, might have utility in the treatment of obesity. In a four week trial with obese participants, sc administration of oxytomodulin three times daily led to a reduction in body weight that was 1.8 kg greater than observed with placebo (Wynne et al., 2005). Subsequently it was shown that oxyntomodulin administration was associated with increased energy expenditure in addition to a reduced food intake (Wynne et al., 2006). It is however too early to predict whether oxyntomodulin administered in this way, would achieve >5% baseline adjusted weight loss in a 1 year trial or meet other criteria for regulatory approval.

5.3. Amylin

The effects of amylin and its analogues on feeding and body weight have been well characterised in both rodents and humans. Studies in rodents have established that amylin has the characteristics that would be expected of an endogenous satiety signal (Lutz, 2006). It decreases food intake through a reduction in meal size, and administration of amylin antagonists leads to enhanced food intake and body weight. The effects of amylin on feeding are mediated via the area postrema in the hindbrain and its projections to nucleus of the solitary tract, the lateral parabrachial nucleus and beyond. There is also substantial expression of amylin receptors in the nucleus accumbens, a critical region for feeding motivation. Infusion of amylin into this area depresses both motor activity and ingestive behaviour (Baldo and Kelley, 2001).

Studies of the effects of amylin receptor activation in humans have utilised peptide analogues such as pramlintide. This drug, like exenatide, improves glycaemic control in diabetes. The acute effect of pramlintide on ingestive behaviour is to reduce energy intake during a freely chosen buffet meal (Chapman et al., 2005). The relative reductions in macronutrient intake were similar in this study and hunger ratings taken through the meal suggested a satiety-inducing effect. A 16 week study comparing pramlintide (twice daily, 240 μg in most participants) and placebo resulted in similar mean reductions in body weight (about 3.6 kg) in participants who either had, or had not, been diagnosed with diabetes. End of study questionnaires demonstrated that pramlintide treatment was associated with a much greater feeling that appetite was under control, and that this benefit was worth the trouble of twice daily injections of the drug. In a larger scale, and more extended, study, the effects of several doses of pramlintide were compared in non-diabetic but obese individuals. The trial was double-blind for 4 months and then continued on a single blind basis for a further 8 months (Smith et al., 2008). Body weight loss at 4 months was comparable to the earlier study. Progressive reductions in body weight were observed at 12 months (placebo corrected weight loss, 120 μg: 6.1 kg; 360 μg: 7.2 kg) which would therefore meet FDA and EMA guidelines for primary efficacy in a weight loss agent.

5.4. NPY and PYY

The complex receptor pharmacology and the mix of orexigenic and anorectic effects that are induced by this peptide family have made them problematic as targets for obesity treatment. NPY was established as a potent central orexigen in the 1980s (Levine et al., 2004), and shown to act in the perifornical hypothalamus (Stanley et al., 1993). A number of lines of evidence indicate that the Y_1 and Y_5 receptors are critical to the effects of NPY on ingestive behaviour (Beck, 2006). The effects of a Y_5 antagonist on body weight have been explored in several recent studies using MK-0557, which is orally available and has greater than 7500-fold selectivity against other NPY receptors (Erondu et al., 2006). A dose-related reduction in the body weight of obese individuals after 12 weeks treatment reached asymptote at 1 mg/kg. A subsequent 52 week study using this dose involved 1661 obese individuals, of whom 832 completed the study. They were given advice about following a diet to induce a daily 500 kcal energy deficit and randomised to placebo or 1 mg MK-0557 on a 1:2 ratio. At 52 weeks, both groups had lost a significant amount of weight, and the difference between placebo and drug was also statistically reliable. However the drug-induced weight loss (placebo: 1.1 kg; MK-0557: 2.2 kg) was

judged to be clinically uninteresting. There were no drug-dependent differences in metabolic syndrome between groups.

Although Y_1 antagonists also represent an obvious target for an obesity treatment, with significant support from both preclinical pharmacological and molecular genetic studies, no human trials have yet been reported.

PYY_{3-36} has attracted considerable interest as a potential starting point for a family of anti-obesity agents. An initial group of preclinical studies in rodents indicated a substantial reduction in acute food intake, and, with chronic treatment body weight (Batterham et al., 2002). However these studies have proved difficult to replicate (Tschöp et al., 2004). Although it has been suggested that these failures reflect inadequate habituation of the experimental animals to the test protocols (Abbott et al., 2006), it seems more likely that administration of PYY_{3-36} has rather complex properties because of its agonist action at Y_1, Y_2 and Y_5 receptors. A recent report substantiates this suggestion by demonstrating an initial anorexigenic effect of PYY_{3-36} followed by an orexigenic effect that is not a simple rebound recovery (Parkinson et al., 2008).

Infusion of PYY_{3-36} reduces food intake in both normal weight and obese humans (Batterham et al., 2003). In this initial study the effects of PYY_{3-36} on consumption of a buffet lunch were compared with placebo using a within subject design. PYY_{3-36} reduced intake in each of 12 obese and 12 lean individuals and also reduced perceived hunger in the period after infusion of the peptide, but before consumption of the test lunch. No long term trials of the effectiveness of PYY_{3-36} have been published, but there is some indirect evidence that the peptide may prove to be an interesting target. Several forms of restrictive bariatric surgery, such as gastric banding, have been used to reduce stomach volume and hence meal size and energy intake. However one variant, the Roux-en-Y gastric bypass, has superior efficacy in both the short and longer germ (Sjöström et al., 2004). This is a surgical procedure that involves creating a small stomach pouch connected directly to the upper gut. The remaining part of the stomach and duodenum are connected to the lower gut. Interestingly the PYY_{3-36}, as well as the GLP-1, response to food is increased, and this enhanced response is maintained for at least 12 months (Korner et al., 2009). Initial attempts were made by Nastech Pharmaceuticals to develop PYY_{3-36} as a nasally administered spray, but results were disappointing and development was subsequently halted.

5.5. Ghrelin

The potent effect of exogenous ghrelin to increase food intake is well established (Castañeda et al., 2009), and a number of recent studies have addressed the behavioural mechanisms that may be involved. Ghrelin is released prior to a meal and several studies suggest that this is, at least in part, a learnt response. Thus, although ghrelin levels peak before expected meals or feeding times, they do not rise in the same way in response to food deprivation, as would be expected if they were a simple correlate of 'hunger' (Drazen et al., 2006). However exogenous administration of ghrelin, or the longer acting ghrelin agonist BIM-28131, reduces the latency to the first meal, increases the size of the first meal, and in the case of BIM-28131, increases subsequent meal frequency (Tabarin et al., 2007). Another effect of ghrelin may be to increase the palatability of food after ingestion begins; studies of licking microstructure following administration of a ghrelin antagonist reduce bout size rather than bout frequency (Johnson et al., 2009). Sub-chronic administration of ghrelin agonists BIM-28125 or BIM-28131 increases food intake and body weight (Strassburg et al., 2008).

These data suggest that ghrelin antagonists, or inverse agonists since the ghrelin receptor has constitutive activity, might be effective in the treatment for obesity. There is limited preclinical evidence to both support and weaken this hypothesis. The selective ghrelin receptor antagonist BIM-28163 unexpectedly leads to an *increase* in body weight although other less selective antagonists have the opposite effect (Castañeda et al., 2009). The novel RNA Spiegelmer NOX-B11-2, which binds selectively and with high affinity to circulating ghrelin and thus inactivates it, blocks ghrelin-induced feeding and promotes weight loss in diet-induced obese mice. There is, however, no published evidence to indicate whether these potential therapeutic routes may be effective in humans. Ghrelin may be implicated in at least a part of the effectiveness of the Roux-en-Y gastric bypass. It has been suggested that this particular procedure is also associated with a substantial decrease the levels of circulating ghrelin but this conclusion remains controversial Diniz et al. (in press).

5.6. MCH

Much effort is currently being committed to the characterisation of novel MCH1 receptor antagonists. Nevertheless, few have entered clinical trials to date. One major issue has been the high affinity of many analogues for the human ether-a-go-go-related gene which encodes a K^+ channel that is critical for heart electrical activity. Binding activity is associated with prolongation of the QTc interval (Mendez-Andino and Wos, 2007). One compound that has been assessed clinically is NGD-4715. In the course of a 2 week multiple ascending dose study in healthy obese subjects where NCD-4715 was administered three times daily for 14 days, plasma lipid levels were observed to fall, but induction of the metabolising enzyme, cytochrome p450 3A4 (CYP 3A4) was also observed. In a second study, using twice daily administration, CYP 3A4 induction was again observed, but the effect on plasma lipids was not replicated. In both studies, although NGD-4715 was relatively well tolerated, sleep disturbance was reported with vivid dreams and awakenings and the development of NGD-4715 was therefore halted (Sargent and Moore, 2009).

5.7. MC4 receptor agonists

The development of MC4 agonists as a target for obesity appears very attractive given the strong biological rationale, particularly the genetic evidence of involvement in human obesity. Accordingly, a large number of drug discovery programmes have been initiated to synthesise such a molecule. The first compound to be placed into clinical trials, bremelanotide, was a peptide derivative of MTII based on the conserved peptide sequence of melanocortin. This peptide has been assessed for the treatment of sexual dysfunction and has not been assessed as a weight loss agent. While bremelanotide appeared to be generally well tolerated in clinical trials, it was associated with flushing, somnolence, nausea, vomiting headache and taste disturbance and some participants experienced severe exacerbation of hypertension (Wikberg and Mutulis, 2008). The latter observation may well reflect the interaction of MC4 and the sympathetic nervous system whereby long term administration of the MC4 agonist, MTII in both normal and obese rats is associated with increased blood pressure and heart rate (da Silva et al., 2006). For these reasons, the FDA has expressed concerns about the cardiovascular safety of bremelanotide and further trials have been halted (Wikberg and Mutulis, 2008). More recently, a non-peptide MC4 agonist, MK-0493, was developed that caused increased energy expenditure and weight loss in diet-induced obese rats. When administered acutely to human subjects in a validated ad-libitum energy intake model at well tolerated doses, only a marginally significant increase in energy expenditure was observed (Krishna et al., 2009). When administered over 12 or 18 weeks to obese subjects in a double-blind, placebo-controlled trial with a 2 week run in period, no significant drug-induced weight loss was observed. The compound was well tolerated with principle adverse events of nausea (16.5% vs 3.6% of controls), diarrhoea and loose stools (37% vs 14% of controls) and skin rash. Interestingly, there were no cardiovascular events, although these had

been observed at higher doses in dogs (Krishna et al 2009). The failure to observe efficacy in the trial with MK-0493 may reflect the use need to use low doses due to tolerability issues. Alternatively it may reflect the presence of high levels of leptin and leptin resistance in obese patients. As one role of leptin is to activate the melanocortin system, leptin resistance may compromise the effect of MC4 agonists (Wikberg and Mutulis, 2008).

6. Monoamine targets and their receptors

The monoamines consist of a group of chemically related compounds that act as neurotransmitters in both the central and peripheral nervous system. Some members of the group, particularly adrenaline, are also important hormones and play a role in integrating metabolic responses to stress and other stimuli. In general the effects of monoamines depend on actions at G-protein-coupled receptors although there are also a few examples of interaction at ion gated channels. Within the central nervous system monoamine projections show many of the signs expected of a neurotransmitter that acts in a modulatory role. Cell bodies are typically relatively small in number and concentrated into rather few anatomical locations. However they typically have extremely broad innervation patterns. Neurotransmitter release may occur at specialised axonal sites, in addition to synaptic release, generating paracrine effects.

6.1. 5-HT

Serotonergic cell bodies are mostly located in the midbrain and hindbrain, particularly in the raphe nuclei. The dorsal and median raphe nuclei, which are found towards the dorsal surface of the midbrain and are also known as cell groups B5-8, are the source of a widespread rostral projection to the forebrain, including areas relevant to feeding such as the hypothalamus and ventral striatum. A more caudal collection of cell groups include the raphe magnus, raphe obscurus and additional serotonergic cells in the ventrolateral medulla, also known as cell groups B1-4, project caudally to the spinal cord and to other hindbrain structures, including potentially feeding-relevant areas such as the parabrachial nucleus, area postrema and nucleus of the solitary tract. The effects of serotonin are mediated by no less than 14 receptor subtypes divided into seven families based on structural and operational similarities. These are classified as 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D}, 5-HT_{1E}, 5-HT_{1F}, 5-HT_{2A}, 5-HT_{2B}, 5-HT_{2C}, 5-HT_3, 5-HT_4, 5-HT_{5A}, 5-HT_{5B}, 5-HT_6 and 5-HT_7 (Barnes and Sharp, 1999). 5-HT_2 and 5-HT_5 receptors exert inhibitory actions by reducing cAMP, while 5-HT_2 receptors are excitatory, mediating their actions via phosphoinositol hydrolysis. All the other subtypes are exert excitatory actions by stimulating cAMP with the exception of the 5-HT_3 receptor which forms an excitatory ligand gated Na+ and K+ cation channel (Barnes and Sharp, 1999). Three subtypes are currently deemed of particular interest in the control of body weight.

The 5-HT_{1B} receptor is distributed widely within the CNS, often as a terminal autoreceptor. There is also significant expression in some hind brain nuclei (e.g. parabrachial nucleus) relevant to feeding. However there is also substantial expression elsewhere in the body, mediating such effects as serotonin-induced constriction of pulmonary arteries (Dempsie and MacLean, 2008).

The 5-HT_{2C} receptor is widely distributed in the mammalian CNS including the amygdala, nucleus accumbens, and the arcuate nucleus of the hypothalamus (Pazos and Palacios, 1985; Lam et al., 2008). The lack of any evidence for functional 5-HT receptors in the periphery provides a rationale for the likelihood of a benign safety profile.

The 5-HT_6 receptor is located exclusively in the brain, particularly in the striatum, although lower levels are found in other areas including the arcuate, lateral, anterior, dorsomedial, paraventricular and ventromedial nuclei of the hypothalamus (Heal et al., 2008).

6.2. Noradrenaline

Noradrenergic and adrenergic cell bodies are mostly found in the hind brain, particularly in the locus coeruleus, and project rostrally to the lateral and medial hypothalamus, hippocampus and cortex. Caudal projections innervate brain stem nuclei (such as nucleus of the solitary tract) areas of the brain that modulate gastric motility, taste or the experience of malaise (Hernandez and Hoebel, 1989; Hoebel et al., 1989).

Adrenergic receptors (ARs) are G-protein coupled and have been divided into two broad classes (α and β) that are widely distributed in the central nervous system.

αARs have been further sub-classified into two families (α_1 and α_2), activation of which produce functionally opposed effects as while α_1ARs are thought to be located postsynaptically and coupled to cyclic AMP, α_2ARs are located presynaptically and function as inhibitory autoreceptors. The α_1AR has three subtypes known as α_{1A}, α_{1B} and α_{1D} and three α_2ARs have also been characterised and are known as the α_{2A}AR, α_{2B}AR, and α_{2C}AR. βARs are classified into three subtypes. β_1 and β_2 ARs are expressed in the central nervous system whereas the expression of β_3 receptors is restricted to the periphery, particularly to brown adipose tissue. Activation of β_3ARs leads to uncoupling of mitochondial ATP production from oxidative metabolism and consequent release of energy as heat. This thermogenic response has received active consideration as an obesity treatment. β_1 ARs are located postsynaptically and are widely expressed in the brain, including areas, such as the hypothalamus, that are relevant to feeding behaviour. β_2ARs are located presynatically but, their activation by contrast with the α_2 receptor, stimulates the release of noradrenaline from the synaptic terminals (Clifton and Kennett, 2006).

6.3. Dopamine

Dopamine is a second catecholaminergic neurotransmitter whose neuronal cell bodies are principally located in the substantia nigra pars compacta (A9) and ventral tegmental area (VTA) (A10). A9 neurons project to the caudate nucleus and putamen forming the nigrostriatal pathway and control motor function, while A10 neuronal projections to the nucleus accumbens, amygdala and hippocampus forms the mesolimbic pathway, while A10 projections to the prefrontal cortex are termed the mesocortical pathway.

Dopamine receptors are classified into two subtype families D_1-like (D_1 and D_5) and D_2-like (D_2, D_3 and D_4) on the basis of pharmacological and structural similarities.

The absence of highly selective pharmacological agents for these subtypes to date, has, however, hindered functional studies, while the location of D_2 receptors both presynaptically, where they act as inhibitory autoreceptors, and postsynaptically, has complicated interpretation of some results (Clifton and Kennett, 2006).

Dopamine D_1 receptors are expressed in cortical areas such as the frontal cingulated, orbital, insular piriform and enterorhinal cortex, some of which influence taste and texture in sensory specific satiety (Rolls, 2005). D_1 receptors are also widely expressed in the striatum, limbic areas, thalamus and hypothalamus.

7. Monoamine targets in the treatment of obesity

7.1. Serotonin (5-HT)

Of the fourteen recognised 5-HT receptor subtypes, the 5-HT_{1B}, 5-HT_{2C} and 5-HT_6 receptors are of most interest for the modulation of body weight.

7.2. 5-HT_{1B} receptors

There is good evidence that 5-HT_{1B} receptor agonists reduce food intake in rodents in a behaviourally selective manner (Clifton and

Kennett, 2006). However, the 5-HT_{1B} receptor agonists currently used for the treatment of migraine, are associated with cardiovascular side effects such as chest pains (Palmer and Spencer 1997) and myocardial infarction (Willet et al., 1992; Lloyd and Simmons, 1993; Ottervanger et al., 1993). These side effects are a consequence of their propensity to contract coronary arteries both pre-clinically (MaasenVanDerBrink et al., 1998) and clinically (MacIntyre et al., 1992). For this reason, no attempt to exploit this target for the development of weight loss agents has been made to date.

7.3. 5-HT_6 receptors

A number of selective 5-HT_6 receptor antagonists and partial agonists have been synthesised and have both demonstrated good hypophagic and chronic weight loss efficacy in rodent studies. The effects of these ligands are apparently behaviourally selective, and 5-HT_6 receptor antagonists appear well tolerated (Heal et al., 2008). However, despite extensive preclinical studies, those 5-HT_6 receptor antagonists currently in clinical trials have been orientated towards other indications such as Alzheimer's disease.

7.4. 5-HT_{2C} receptors

5-HT_{2C} receptor knockout mice are hyperphagic and become obese from 5 to 6 weeks old, progressively exhibiting symptoms of type II diabetes (Nonagaki et al., 1998). This suggests that the 5-HT_{2C} receptor is tonically activated under normal conditions to suppress food intake.

There is also good evidence that pharmacological activation of 5-HT_{2C} receptors can reduce feeding and perhaps other forms of motivated behaviour such as drug self administration. In rodents, 1,3, chlorophenylpiperazine (mCPP), a 5-$HT_{2C/1B}$ receptor agonist, provided early evidence for 5-HT_{2C} receptor mediated reductions in food intake (Kennett and Curzon, 1988). The effects of mCPP on feeding behaviour are attenuated by pretreatment with the selective 5-HT_{2C} receptor antagonist SB242084 in both rats (Kennett et al., 1997b) and mice (Hewitt et al., 2002) and are also reduced in 5-HT_{2C} receptor knockout mice (Heisler et al., 1998). In humans, mCPP reduces both rated appetite and food intake (Sargent et al., 1997). A second 5-HT_{2C} receptor agonist, Ro 60-0175 (Porter et al., 1999) also reduces food intake in rats in a behaviourally selective manner (Clifton et al., 2000) and the effect is blocked by pretreatment with SB242084 in both rats (Clifton et al., 2000) and mice (Hewitt et al., 2002). A number of other putatively selective 5-HT_{2C} receptor agonists have now been described including BVT.933 (Biovitrum/GlaxoSmithKline), YM348 (Yamamouchi), VER-23779/RO-4590334 (Vernalis/Roche) (Monck and Kennett, 2008). Experimental human, rodent and other animal studies indicate that activation of 5-HT_{2C} receptors enhanced the development of satiety during a meal (Clifton and Kennett, 2006). A series of recent studies has indicated that the hyophagic effects of 5-HT_{2C} agonists are largely mediated by 5-HT_{2C} receptors on proopiomelanocortin (POMC) neurons in the arcuate nucleus of the hypothalamus which modulate the release of α-melanocyte stimulating hormone (α-MSH), an endogenous agonist of the MC_4 receptor (Lam et al., 2008; Xu et al., 2008) which has an inhibitory effect on feeding behaviour.

The likelihood that 5-HT_{2C} receptor ligands would be effective treatments for obesity is supported by evidence that the clinically effective anorectic agents, fenfluramine and its more active isomer, dexfenfluramine, elicit weight loss via the formation of an active metabolite, d-norfenfluramine, with potent 5-HT_{2C} receptor agonist properties (Porter et al., 1999; Fitzgerald et al., 2000). Thus, the hypophagic effects of dexfenfluramine are blunted in 5-HT_{2C} receptor null mutant mice (Vickers et al., 1999) and are inhibited by selective 5-HT_{2C} receptor antagonists, but not by antagonists of other 5-HT receptor subtypes (Vickers et al., 2001). Consistent with rodent studies, the hypophagic action of dexfenfluramine in humans is attenuated by the non-selective 5-HT_{2C} receptor antagonist, ritanserin (Goodall et al., 1993). A clinical trial meta-analysis has concluded that the expected weight loss with racemic fenfluramine was a relatively (by comparison to sibutramine or the >5% placebo-controlled weight loss now required by the FDA and EMA) modest 2.4 kg better than placebo in completers (Haddock et al., 2002) while dexfenfluramine, elicited a more substantial mean of 3.8 kg weight loss over placebo in trial completers over 4–56 weeks (Haddock et al., 2002). This degree of weight loss was however much improved to approximately 10% when dexfenfluramine was prescribed in combination with phentermine (see Section 11). However, widespread use of the combination therapy was associated with the development of valvulopathy (Connolly et al. 1997) resulting in the withdrawal of dexfenfluramine in 1997. The risk of primary pulmonary hypertension (PPH) was also a focus of some concern. Both valvulopathy (Fitzgerald et al., 2000; Roth, 2007) and PPH (Launay et al., 2002) are now considered a consequence of activation of the mitogenic 5-HT_{2B} receptor at which d-norfenfluramine has substantial activity (Fitzgerald et al., 2000; Roth, 2007). Selectivity over the 5-HT_{2A} receptor is also necessary as activation of this subtype is hallucinogenic (Nichols, 2004).

These studies have led a number of groups to develop selective 5-HT_{2C} receptor agonists. However, it has proved difficult to develop compounds with the required selectivity between 5-HT_{2C} and other receptor subtypes, especially the 5-HT_{2B} and 5-HT_{2A} receptors.

7.5. Lorcaserin

Lorcaserin is the most advanced compound in development for obesity that targets the 5-HT_{2C} receptor. Lorcaserin has high affinity for the h5-HT_{2C} receptor (Ki = 15 nM), but modest binding selectivity against the closely related h5-HT_{2A} (7.5 fold) and h5-HT_{2B} (11.6 fold) receptors, and indeed, the 5-HT_{1A} (24.1 fold) and 5-HT_7 (21.9 fold) receptors, although the compound has >100 fold selectivity over all other receptor subtypes at which it has been profiled. However, the true selectivity of this molecule is related to its agonist potency and efficacy. At the 5-HT_{2C} receptor, lorcaserin acts as a full agonist with an EC_{50} of 9 nM in transfected cells expressing the 5-HT_{2C} receptor. At the h5-HT_{2A} receptor, the compound had an EC_{50} of 168 nM and acts as a partial agonist (75% efficacy), while at the 5-HT_{2B} receptor the compound has low potency (EC_{50} 943 nM) and acts as a full agonist. Thus, in efficacy tests, lorcaserin has 18.6 fold selectivity over the 5-HT_{2A} receptor and 105 fold selectivity over the 5-HT_{2B} receptor. Efficacy at the 5-HT_{1A} and 5-HT_7 receptors has not been reported to date (Thomsen et al., 2008). As 5-HT_{2A} receptor agonists are hallucinogenic (Nichols, 2004), while 5-HT_{2B} receptor activation is mitogenic and associated with the development of valvulopathy (Fitzgerald et al., 2000; Roth, 2007) and PPH (Launay et al., 2002), any 5-HT_{2C} agonist for the treatment of obesity must achieve adequate selectivity over these subtypes. Unfortunately, the assessment of the therapeutic ratio of agonists is not straightforward as it depends upon functional data obtained from artificial cell systems whose coupling efficiency, expression density and effector mechanisms may well differ from those of the relevant receptor populations responsible for efficacy or safety concerns in humans. In vivo assessment in humans may therefore be necessary to evidence the true safety margins. One factor that may promote the safety margin of lorcaserin is its high brain plasma ratio (13.3) (Thomsen et al., 2008) although it is unclear whether plasma levels are necessarily a more relevant tissue pool than heart or pulmonary tissue exposure.

Lorcaserin was assessed in a double-blind, placebo-controlled Phase II study of 469 obese men and women (Body Mass Index (BMI) 30–45 kg/m^2) over 12 weeks without diet restriction or lifestyle modification. In this study, lorcaserin administered at a dose of 10 or 15 mg once daily or 10 mg/kg bid, elicited progressive placebo-adjusted weight loss of 1.5, 2.0 and 2.9 kg respectively, using an intention to treat, last

observation carried forward (ITT LOCF) analysis. Echocardiogram readings during the trial detected no effect of the compound on heart valves or pulmonary artery pressure (Smith et al., 2009).

Two Phase III studies have now been completed. The first, "Bloom" was a double-blind, placebo-controlled study in which 3182 obese patients (BMI of between 30 and 45 kg/m^2) with or without co-morbidities and overweight patients (BMI 27–30 kg/m^2) with at least one co-morbidity, were treated with placebo or lorcaserin 10 mg/kg bid for 2 years. All subjects were on a restricted diet with lifestyle modification, but there was no run in period prior to the initiation of dosing. At the end of the first year, following an ITT LOCF analysis, obese patients had lost 3.6 kg (3.6% body weight) more than controls. The proportion of patients losing >5% body weight was 47% in lorcaserin treated patients vs 20.5% of controls. The corresponding figure for >10% weight loss was 22.6% for lorcaserin vs 7.7% of controls (Smith et al., 2010; Arena Pharmaceuticals Inc press release, March 30th, 2009). Following the first year of this trial, lorcaserin treated patients were either maintained on lorcaserin or switched to placebo. In those patients that had achieved >5% weight loss during year 1, and were maintained on treatment during year 2, a significantly ($P<0.001$) higher percentage retained their weight loss (67.9%) than those switched to placebo (50.3%). Thus whilst weight regain occurred during the second year of lorcaserin treatment, this was restrained when compared to those withdrawn from treatment (Smith et al., 2010).

In a second trial of similar design over 1 year, termed "Blossom" 4008 patients were treated with lorcaserin 10 mg qd or bid. At the end of 12 months, using an ITT LOCF analysis, lorcaserin 10 mg bid treated patients had achieved 3.1% placebo-adjusted body weight loss. The proportion of patients on this dose achieving ≥5% weight loss was 47.2% vs 25% of placebo-treated controls and the corresponding figures for ≥10% weight loss were 35.1% vs 16.1% respectively (Arena Pharmaceuticals Inc, press release Sept 18th, 2009). Whilst weight loss in both the Bloom and Blossom trials is less than the placebo corrected 5% over 6 months to 1 year required by the FDA and EMA, the proportion of patients achieving 5% weight gain is >35% and this is > double the number of placebo responders. Thus lorcaserin would appear to meet the primary efficacy endpoint required by the FDA at least. The proportion of patients treated with lorcaserin who lost 10% body weight was 22.6 vs 7.3% of placebo controls and this may satisfy current European criteria.

There were modest but significant placebo-adjusted improvements in HbA1c (−0.7%) total cholesterol (−1.5%), plasma triglycerides (−6.0%) blood pressure (−0.6 mm Hg systolic and −0.5 mm HG diastolic blood pressure) and heart rate (−0.4 bpm) in the Bloom trial, but similar magnitude effects on cardiovascular parameters were not significant in the Blossom trial and have yet to be reported for other measures. Echocardiogram monitoring found no evidence that lorcaserin treatment had affected valvular function over either one (Smith et al., 2010; Arena Pharmaceuticals Inc, press release Oct 27th, 2009) or 2 years (Smith et al., 2010). Despite these positive findings, care will still be needed to ensure safety, should lorcaserin be administered to a wider patient population, where lower incidences of valvulopathy or PPH and may become apparent. The drop-out rate for lorcaserin treated patients in the Phase III studies has not been disclosed to date, although in the 12 week Phase II study, lorcaserin (10 mg bid) was relatively well tolerated with a discontinuation rate of 34% compared to 26% of controls (Smith et al., 2009). Major adverse events in the Phase III studies were 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 (Arena Pharmaceuticals Press release Oct 27th, 2009). There was no evidence that lorcaserin caused anxiety in spite of the association of non-selective 5-HT$_{2C}$ agonists with anxiety in preclinical and clinical studies (see Monck and Kennett, 2008). Neither did lorcaserin elicit depressed mood which, given the ability of 5-HT$_{2C}$ receptor agonists to reduce mesolimbic dopamine and hence reward function in rats (Monck and Kennett, 2008), is a potential risk for this approach. Indeed, when lorcaserin 20 mg was assessed by recreational drug abusers, the compound was experienced either as neutral or with significant dislike at supratherapeutic doses (Arena Pharmaceutical Inc Press release, Dec 10, 2009), which may at least in part reflect modulation of reward function.

It is concluded that lorcaserin meets the stated FDA efficacy requirements as a weight loss agent although as for other weight loss treatments, withdrawal is associated with weight regain. Lorcaserin also appears to be well tolerated with no evidence of major safety issues, but the risk of PPH or indeed the risk of valvulopathy may only be fully appreciated on exposure to a larger patient population and possibly over a longer time frame than current studies. Lorcaserin-induced weight loss efficacy is also relatively modest when compared to either sibutramine, the fenfluramine and phentermine combination therapy or other agents in development (see Table 3) and no better than that obtained with dexfenfluramine alone (Haddock et al., 2002). The utility of lorcaserin might best be promoted by co-administration with another weight loss agent. Lorcaserin is to be reviewed by an FDA advisory panel on September 16th 2010.

7.6. Noradrenaline

Consistent with the opposing roles of α_1 and α_2 adrenoceptors within the noradrenergic system, these subtypes exert opposing actions on feeding and body weight. Thus, pharmacological studies suggest that α_1AR agonists may reduce feeding (Morien et al., 1993), at least in part by activation of receptors located in the hypothalamus (Wellman and Davies, 1991, 1992). By contrast, activation of α_2ARs particularly by infusion into the paraventricular nucleus of the hypothalamus increases feeding by increasing meal size but leaves meal frequency unaffected (Shor-Posner et al., 1998). An α_2AR antagonist, idazoxan, had the opposite effect when administered systemically or infused into the paraventriclar nucleus (Alexander et al., 1993).

Although knockout mice have been generated for all of the receptors subtypes described above, none have yet been reported to show altered food intake or body weight (Clifton and Kennett, 2006). Of the β adrenergic receptor knock outs, null mutants for the β_1 receptor have no disturbance of body weight (Rohrer et al., 1996), but β_2 knockout mice are some 10% lighter than their wild type littermates with smaller epididymal fat pads, and show enhanced responding in situations of forced exercise using a treadmill (Chruscinski et al., 1999).

Given the role of the noradrenaline in the endogenous modulation of feeding, it is unsurprising that a number of clinically used drugs that reduce appetite also act via this system, including amphetamines which are potent noradrenaline releasers although perhaps better known for their ability to enhance dopaminergic function (Christensen et al., 2007). These amphetamine-related compounds such as amphetamine itself, phenylpropanolamine (PPA) and ephedrine (EP) have sympathomimetic and psychostimulant properties (Craddock, 1976). Amphetamine was used clinically as an appetite suppressant until the 1970s when it was withdrawn because of its abuse potential (Craddock, 1976). PPA and EP were used until recently in over the counter products, but have now been withdrawn because of their association with primary pulmonary hypertension (Abenheim et al., 1996), stroke and heart disease (Kushner and Manzano, 2002). However, casual use of these drugs, and also of cocaine, is still thought to be prevalent as a method of controlling body weight. More recent drugs that utilise noradrenergic mechanisms (although not exclusively as discussed below) to control body weight include sibutramine (a noradrenaline and 5-HT reuptake inhibitor), phentermine (a noradrenaline and dopamine releasing agent), bupropion (a noradrenergic and dopamine reuptake blocker) and tesofensine (a noradrenaline, dopamine and 5-HT reuptake inhibitor). Of these, only sibutramine acts independently of the dopamine system.

Table 3
Efficacy of novel treatments for obesity in clinical trials using an intention to treat, last observation carried forward (ITT LOCF) analysis.

Treatment	Dose	n	Run in period	Diet and lifestyle changes	Trial duration (weeks)	Placebo-adjusted wt loss kg (%)	% of drug treated (placebo) achieving criteria weight loss		Drop out rate (placebo)	Study
							>5%	>10%		
Lorcaserin	Lorcasersin 10 mg bid	459	No	No	12	2.9 kg (2.9%)	31% (2%)	0% (0%)	30% (24%)	Smith et al., 2008
		3182	No	Yes	52	3.6 kg (3.6%)	47% (20%)	23% (8%)	45% (55%)	Smith et al., 2010; Bloom[a]
		4008	No	Yes	52	3.1 kg (3.1%)	47% (25%)	23% (10%)	43% (28%)	Blossom[b]
Tesofensine	Tesofensine 0.25 mg	203	Yes	Yes	24	4.5 kg (4.5%)	59% (29%)	35% (7%)	19% (27%)	Astrup et al., 2008b
	Tesofensine 0.5 mg					9.1 kg (9.0%)	87% (29%)	53% (7%)	16% (27%)	
Zonisamide	Zonisamide dose titrated up to 600 mg	60	No	Yes	16	5.0 kg (5.0%)	57% (10%)	23% (0%)	44% (37%)	Gadde et al., 2003
	Zonisamide SR 360 mg	70–90	nr	Yes	24	nr (3.90%)	nr	nr	nr	Orexigen Sept 30 2009
Rimonabant	Rimonabant 20 mg	4110	Yes	Yes	52	4.7 kg (4.7%)	51% (19%)	26% (7%)	41% (42%)	Christensen et al., 2007; Van Gaal et al., 2008
Taranabant	Taranabant 2 mg	2502	Yes	Yes	52	4.1 kg (4.1%)	60% (27%)	28% (8%)	36% (41%)	Aronne et al., 2010a
		1041	Yes	Yes		5.0 kg (5.0%)	53% (24%)	28% (7%)	34% (34%)	Proietto et al., 2010
		623	Yes	Yes	52	2.9 kg (3.1%)	52.3(27.6)	17% (5%)	25% (27%)	Kipnes et al., 2010
Metraleptin + pramlintide	Pramlintide 360ug + Metraleptin 5 mg	177	Yes	Diet	20	10.2 kg (10.7%)†	89%(n/a)	58% (n/a)	32% (n/a)	Ravussin et al., 2009
Contrave	Bupropion SR 400 mg + Naltrexone IR 32 mg	419	Yes	Yes	24 48	4.4 kg (4.6%)	51% (15%)	27% (3%)	36% (32%)	Greenway et al 2009b
						6.3 kg (6.6%)†	51% (n/a)	25% (n/a)	46% (n/a)	
		982	Yes	Yes	52	nr	nr	25 (7%)	26% (13%)	COR I[c]
		709	Yes	Yes	52	nr	nr	33% (6%)		COR II[c]
Empatic	Bupropion SR 360 mg + Zonisamide SR 360 mg	729	nr	Yes	24	nr (6.1%)	60% (15%)	32% (4%)	34% (29%)	Orexigen Sept 30 2009
Qnexa	Phentermine 15 mg +	756	Yes	Yes	24	7.5 kg (7.5%)	66% (15%)	41% (7%)	29% (nr)	Equate[d]
	Topiramate SR 92 mg	1267	Yes	Yes	52	10.9 kg (9.4%)	67% (17%)	60% (nr)	41% (nr)	Equip[d]
		2487	Yes	Yes	52	8.9 kg (8.6%)	70% (21%)	64% (nr)	36% (43%)	Conquer[d]

ns = not significant, nr = not reported, n/a = not applicable, *in subgroup whose baseline HbA1C>8.0%, †Not placebo-adjusted.
[a] Arena Pharmaceuticals Inc press release, March 30th, 2009.
[b] Arena Pharmaceuticals Inc, press release Sept 18th, 2009.
[c] Orexigen Therapeutics Inc Press release Oct 27th 2009.
[d] Vivus Inc press release, September 9th.

7.7. Sibutramine

Sibutramine is a mixed noradrenaline/serotonin reuptake agent (Bray et al., 1999) which is currently approved in North America for the treatment of obesity, and is thought to exert on feeding through indirect stimulation of adrenergic and serotonergic receptors such as the 5-HT_{2C} site. Indeed, the two mechanisms are thought to act synergistically (Heal et al., 1998). Sibutramine suppresses food intake, but also enhances thermogenesis via β_3-receptor activation in rats at least, as brown adipose tissue is not a major controlling factor in human thermogenesis (Heal et al., 1998). Sibutramine is currently the most efficacious weight loss agent marketed and can elicit 4.5% body weight loss over 24–52 weeks (Li et al., 2005). However, as discussed above, sibutramine has recently been withdrawn from the European market following a recent review by the EMA of initial results from a 5 year Sibutramine Cardiovascular OUTcome Trial (SCOUT) in obese patients with a high risk of cardiovascular disease. Preliminary analyses of data from this trial indicated that 11.4% of patients taking sibutramine experienced serious cardiovascular events such as non-fatal heart attacks and strokes, as against 10% in those receiving placebo. The available study data also demonstrated that long term weight loss with sibutramine was modest and was reversed on drug withdrawal. EMA therefore concluded that the benefits of the drug as a weight loss therapy did not outweigh its risks (EMA press release 21/1/2010). It should however be noted that the patient group utilised for the SCOUT study is normally contraindicated for sibutramine due to its known propensity at therapeutic doses to increase heart rate and to increase systolic and diastolic blood pressure by a highly significant 1.6 and 1.8 mm Hg respectively (Hansen et al., 1999; Kim et al., 2003).

7.8. Dopamine

Dopamine can influence feeding behaviour in a variety of ways. For instance, dopamine within the olfactory bulbs can influence sensory perception of food, while dopamine projections to the nucleus tractus solitarius and area postrema may influence food intake through the induction of malaise and control of gut motility. Alternatively, projections from the midbrain A9 and A10 cell groups to the striatal and limbic areas of the brain may influence voluntary motor activity, alertness and importantly reward function. Indeed, it is thought that the pleasurable effects caused by the release of dopamine may override normal satiety mechanisms, while animals with deficient dopamine may starve to death presumably due to a failure to learn the value of food. Finally, dopamine projections to the paraventricular and arcuate nuclei of the hypothalamus may directly affect food intake mechanisms (Clifton and Kennett, 2006).

Stimulation of D_1 receptors with D_1 selective agonists suppressed feeding in both food-deprived (Terry and Katz, 1994) and palatable meal-induced (Al-Naser and Cooper 1994) feeding and reduced meal size in freely-feeding rats (Cooper et al., 2006). In the study of Terry and Katz (1994), this was opposed by a D_1 selective antagonist. However, as D_1 agonists also reduce locomotor activity at similar doses to those that suppress food intake (Isacson et al., 2004), the behavioural specificity of these effects is uncertain. A further difficulty in comprehending the role of D_1 receptors in feeding is posed by evidence that D_1 receptor antagonists such as SCH23390 also suppress food intake of both food-deprived rats (Gilbert and Cooper, 1985) and rats engaged in food-rewarded operant behaviour (Nakajima, 1989), although as D_1 antagonists suppress other reward related behaviours, the effect on feeding may not be specific (Nakajima, 1989). Consistent with a role for D_1 receptors in modulation of feeding behaviour, adult D_1 knockout mice have reduced body mass compared with wild type controls (Drago et al., 1994).

Two splice variants of the D_2 receptor have been observed, with the short form (D_{2S}) being located on dopamine cell bodies where it functions as an inhibitory autoreceptor, while the longer variant, (D_{2L}) is found on postsynaptic locations in the limbic system and striatum. Unlike D_1 receptors, several selective D_2 receptor selective ligands have

been characterised and some have been used to investigate the functional significance of D_2 receptors. In microstructural studies, the selective D_2 receptor agonist, N-0437 reduced food intake, in a manner consistent with enhanced satiety. In meal patterning studies however, only higher doses reduced food intake, while low doses increased it (Clifton et al., 1989), possibly due to autoreceptor-mediated inhibition of dopamine release. The effects of D_2 receptor antagonists are also complex as high doses reduce feeding probably due, at least in part, to sedation and catalepsy, while lower doses which do not elicit motor effects also reduce feeding particularly those associated with anticipatory responding to food related cues (Drago et al., 1994). In meal patterning studies, antagonists such as pimozide, nemonapride, raclopride and haloperidol increase meal size, but decrease meal frequency and inter-meal feeding (Clifton and Kennett, 2006).

There is little evidence for D_3, D_4 or D_5 modulation of feeding or body weight (Clifton and Kennett, 2006). The development of agents that utilise dopamine as a principle mechanism of action has been limited by the risk of dopaminergic side effects. D_2 receptor agonists such as apomorphine, bromocriptine or ropinirole cause nausea and vomiting due to their presence in the NTS and AP. They are also associated with postural hypotension and sleep attacks. Finally, D_2 receptor agonism elicits psychosis, hallucinations and stimulant activity giving rise to abuse potential. The occurrence of such effects (Craddock 1976) has led to the withdrawal of amphetamine-like compounds. It is however possible to reduce such effects by the use of partial agonists or mechanisms that result in less pronounced elevations of extraneuronal activity.

Drugs that utilise dopaminergic mechanisms to control body weight include phentermine a noradrenaline and dopamine releasing agent, bupropion, a noradrenergic and dopamine reuptake blocker and tesofensine, a noradrenaline, dopamine and 5-HT reuptake inhibitor.

7.9. Phentermine

Phentermine is thought to act via the release of both noradrenaline and dopamine (Rothman et al., 2001) and has been widely used as monotherapy for the treatment of obesity. A meta-analysis of its efficacy concluded that a significant but modest (when compared to its use in combination with fenfluramine or with examples in Table 3) mean weight loss of 3.6 kg greater than placebo might be expected using doses of between 15 to 30 mg when combined with lifestyle modification for up to 24 weeks (Li et al., 2005). Given the role of the sympathetic nervous system in modulating the cardiovascular system, it is unsurprising that the use of phentermine is associated with palpitations, tachycardia, increased blood pressure, arousal, headaches and gastrointestinal (GI) effects (Li et al., 2005). Also due to its amphetamine-like action, phentermine is considered to have abuse potential (Craddock, 1976; Silverstone, 1992) and is included on the US Drug Enforcement Agency schedule at level IV, although it is not equivalent to that of amphetamine which is listed at level II. Phentermine is also thought to engender tolerance development (Li et al., 2005). For these reasons phentermine is only approved for short term use in the US and has been removed from the market in Europe.

7.10. Bupropion

More recently, dopamine reuptake inhibitors have been investigated for use as weight loss agents. The most studied of these is the dopamine and noradrenaline reuptake inhibitor, bupropion. Bupropion was originally developed as an anti-depressant and has proved to be both clinically effective and well tolerated with little of the abuse potential associated with more vigorous stimulants of dopamine function (Teller et al., 1997; Zernig et al., 2004). As anticipated from its pharmacological profile, bupropion is reported to suppress appetite and food cravings in man (Anderson et al., 2002) although a recent study has reported that weight loss is largely accounted for by increased energy expenditure rather than reduced energy intake (Billes and Cowley, 2008). Despite inhibiting noradrenaline as well as dopamine reuptake, bupropion has little effect on cardiovascular function (Taylor, 2008; Thase et al., 2008), unlike sibutramine. Bupropion may however cause depressed mood and suicidality in man or adolescents (Ayers and Tobias, 2001) when overdosed. It is also associated with the induction of seizures (Spiller et al., 1994) and for this reason is contraindicated in patients with a history of seizures or in bulimics, who appear to be particularly sensitive to bupropion-induced seizures (Horne et al., 1988). Given the greater cardiovascular safety margin of bupropion, it is unfortunate that it has proved only modestly effective as a weight loss agent and a meta-analysis of bupropion studies concluded that over 24–52 weeks, an average weight loss of only 2.8 kg was achieved (Li et al., 2005). This is insufficient to meet the current regulatory criteria that $\geq$5% weight loss is required for marketing approval. In part, the lack of efficacy may be due to the rapid development of tolerance (Greenway et al., 2009a).

7.11. Tesofensine

Tesofensine is an inhibitor of noradrenaline, dopamine and serotonin reuptake that is also reported to indirectly stimulate the cholinergic system (Thatte, 2001) although the full details of its pharmacological profile are not widely available. This compound was originally developed for treatment of Alzheimer's (AD) and Parkinson's (PD) diseases, but although little efficacy was noted in clinical trials for these indications, persistent weight loss was evident. A meta-analysis was conducted on the results from 967 patients over 14 weeks of tesofensine administration once daily in two phase II studies for AD and two phase II studies in PD. As these studies were not designed to examine beneficial changes in body weight, diet restriction, lifestyle modification and the inclusion of a run in period prior to trial initiation were not enforced. Furthermore, the patient groups were predominantly non-obese with BMI$<$30 kg m^2. Nevertheless, tesofensine was found to cause a modest placebo-adjusted weight loss of 1.8 kg or 2.5 kg at doses of 0.5 or 1 mg/kg respectively based on completer values. In a subgroup analysis of all patients whose BMI was $\geq$30 kg/m^2, tesofensine-induced weight loss rose to 1.6 and 3.6 kg respectively (Astrup et al., 2008a). A proof of concept Phase II study was therefore initiated. This randomized double-blind placebo-controlled study was conducted in 203 diet-restricted obese patients (BMI 30–40 kg m^2) over 24 weeks following a 2 week run in period. Following a modified ITT LOCF analysis, placebo-adjusted body weight reductions for tesofensine 0.25, 0.5 and 1 mg dose levels were an impressive 4.5 (4.4%), 9.1 (9.0%)and 10.6 (10.4%) kg respectively. Furthermore, the proportion of patients achieving $>$5 kg (4.9%) was 59%, 87% and 91% for 0.25, 0.5 and 1 mg groups respectively compared with 29% of controls. Corresponding $\geq$10 kg (9.7%) weight loss was achieved by 35%, 53% and 74% respectively, compared to 7% of placebo-treated controls (Astrup et al., 2008b). The majority of weight loss achieved was in body fat. Indeed, a double-blind 14 day study of tesofensine administration in obese subjects reported increased fat, but not protein metabolism, increased night time energy expenditure and reduced appetite as determined by subjective visual analogue scale scores (NeuroSearch A/S press release 11th August, 2008). These findings are consistent with evidence that monoamines lower appetite while noradrenaline is also associated with increased metabolic rate and β-oxidation (See Section 7.6). Only very modest effects on HbA1C were observed. It is however possible, given the lag period required to observe HbA1C level fluctuations, that a more profound effect might emerge from more prolonged studies. Tesofensine administration also improved lipid profiles with reduced triglycerides and total cholesterol, although neither high density lipoprotein (HDL) nor low density lipoprotein (LDL) levels were consistently altered (Astrup et al., 2008b).

Tesofensine appeared well tolerated for a study of this kind with 71% of those treated with the highest dose completing the 24 week study and 20% withdrawing due to adverse events. These were most frequently dry mouth (possibly reflecting the action of tesofensine on cholinergic function), nausea, dizziness, abdominal pain and constipation. Given the use of monoamine reuptake inhibitors as antidepressants, there was, unsurprisingly, no evidence of depressed mood. Indeed, a more relevant concern for any treatment that enhances dopamine and noradrenaline is that, like amphetamines, it may have abuse potential. However, tesofensine was deemed to lack abuse potential in a trial involving recreational stimulant users (NeuroSearch A/S press release 7th May, 2009). Indeed, some patients treated with tesofensine experienced increased anxiety.

A greater concern, however, of drugs that enhance catecholaminergic function, is that they may affect cardiovascular parameters in a similar manner to sibutramine and phentermine (See Section 7.7). In the meta-analysis of Astrup et al. (2008a), tesofensine was associated with a dose-dependent increase in heart rate of up to 6.0 or 6.8 bpm for the 0.5 and 1 mg treated groups respectively having reached a plateau over 14 weeks. These findings were confirmed in the 24 week obesity trial (Astrup et al., 2008b) where 0.5 mg tesofensine elicited a 7.8 bpm increase vs 8.5 for the 1 mg dose. Concurrent systolic and diastolic blood pressure increases were limited to between 1 and 2 mm Hg and did not reach significance in the meta-analysis of non-obese subjects. In the subsequent study of an obese subject population over a longer time span, tesofensine 1 mg caused a significant 6.8 mm Hg increase in systolic and 5.8 mm Hg increase in diastolic blood pressure. Presumably to reduce the risk associated with the 1 mg dose, it has been reported that the Phase III program agreed with the FDA will assess the 0.5 and 0.25 mg dose levels only (NeuroSearch S/A press release, 8th June, 2009). It remains to be seen if the cardiovascular risk can be eliminated when lower doses are administered to a larger population of obese subjects and, if so, whether significant weight loss efficacy can be retained.

8. Anticonvulsants and the treatment of obesity

The clinical use of anticonvulsants is generally associated with weight gain. However, zonisamide and topiramate unexpectedly elicit weight loss in clinical trials. For this reason, they have been investigated for their utility as weight loss agents.

8.1. Zonisamide

Zonisamide is a marketed anti-epileptic treatment thought to exert its anti-epileptic actions via the blockade of calcium (T-type) and sodium channels (Oommen and Mathews, 1999). However, unlike other anticonvulsants such as carbamazepine with a similar mechanism of action, zonisamide was found to cause weight loss in man (Oommen and Mathews, 1999), beagles (Walker et al., 1988) and rats where weight loss was associated with a loss of feeding efficiency (Wallingford et al., 2008). While initially considered an adverse event (Oommen and Mathews, 1999), zonisamide has now been evaluated as a potential weight loss treatment. In an initial double-blind clinical trial in 60 diet-restricted obese subjects with a starting BMI of 36.3 kg/m^2 over 16 weeks, Gadde et al. (2003) observed that administration of up to 400 mg daily zonisamide up to week 12 and to 600 mg daily for poor responders, was associated with a 5.0 kg (5%) placebo-adjusted weight loss using an ITT, LOCF analysis. Fifty seven percent of subjects on zonisamide achieved >5% weight loss vs 10% of controls which therefore meets FDA and EMA primary endpoint weight loss guidelines. Zonisamide was well tolerated in this study with only 2 subjects out of 30 withdrawing due to adverse events although only 57% of subjects completed the 16 week study compared with 63% of controls. Fatigue was the principle adverse event. Zonisamide has also elicited modest weight loss in schizophrenics (Yang et al., 2010) and epileptics (Welmer et al., 2009) and has been the subject of trials in binge eating disorder (McElroy et al., 2004, 2006). In the study of McElroy et al. (2006), zonisamide administration, using a similar dosing regimen to that of Gadde et al. (2003), was poorly tolerated in a limited number of subjects (12) due to high levels of cognitive and psychological impairment. These in turn may have led to the observed high incidence of bone fractures, through accidental injuries. Zonisamide is also associated with a mood disorders such as depression (Mula and Sander, 2007) and may have teratogenic potential (Ohtahara and Yamatogi, 2004; Leppik, 1999). Further clinical studies of zonisamide using a sustained release formulation are underway to ascertain whether it could be used as an anti-obesity monotherapy.

The mechanism of action of zonisamide-induced weight loss is uncertain. At doses that are anticonvulsant in rodent models, zonisamide increases extraneuronal dopamine, (Okada et al., 1995; Yamamura et al., 2009) noradrenaline (Yamamura et al., 2009) and serotonin (Okada et al., 1999; Yamamura et al., 2009) in rat hippocampus, effects that are reversed after administration of supramaximal doses. Zonisamide also directly activates dopamine D2 receptors (Okada et al., 1995) and can weakly block monoamine oxidase (MAO) A and B (Okada et al., 1995). As increased levels of dopamine and serotonin metabolites are observed after zonisamide treatment, the action of zonisamide on MAO is unlikely to play an important role. In contrast, the ability of zonisamide to increase GABA release (Yamamura et al., 2009) may act to negate monoaminergic-induced weight loss as GABA agonists stimulate feeding behaviour (Meena et al., 2009) and are associated with clinical weight gain (e.g. Valentin et al., 2009). One other possible mode of action may be derived from zonisamide's potent (KI 35 nM) time-dependent inhibition of carbonic anhydrase (De Simone et al., 2005), an enzyme which can regulate de novo lipogenesis (De Simone et al., 2008) and which is also reported to affect taste (Dahl et al., 1984).

8.2. Topiramate

The mode of action of topiramate is also uncertain. Like zonisamide, topiramate is thought to exert is anticonvulsant actions via effects on sodium and calcium (T-type) channels, a mode of action that is not associated with weight loss in drugs such as carbamazepine. Furthermore, like zonisamide, doses of topiramate that are anticonvulsant in rats increase extraneuronal levels of dopamine, noradrenaline and 5-HT in the hippocampus (Yamamura et al., 2009). If similar effects occur in the hypothalamus, they could account for the hypophagic actions of topiramate (Richard et al., 2000). In addition to monoamine-mediated appetite suppression, a strong body of preclinical literature suggests that topiramate also increased fat metabolism. This results from increased activity of lipoprotein lipase, in both white and brown adipose tissue (Richard et al., 2000, 2002) which inhibits fat deposition and promotes thermogenesis. Alternatively, a DNA microarray study of female ZDF rats, has suggested that topiramate can elicit a pattern of changes in mRNA level of key enzymes to promote hepatic fat metabolism and decrease fatty acid synthesis (Liang et al., 2006). The use of pair-fed controls in the Liang et al. (2006) study indicated that these changes were not merely a consequence of reduced food intake. A third possible mechanism of action of topiramate, and one shared with zonisamide, is derived from its potent inhibition of carbonic anhydrase II (KI 5.4–15.4 nM) and V (KI 20.6–25.4 nM), thereby inhibiting lipogenesis (De Simone et al., 2005; 2008). The effect of topiramate on carbonic anhydrase may contribute to topiramate-induced hypophagia via altered taste sensitivity (Dahl et al., 1984). Indeed, the latter has been reported in clinical trials of topiramate, but appears to affect only a small proportion of patients (Li et al., 2005). Finally, in studies of insulin receptor sensitivity, topiramate was found to increase glucose uptake into adipose tissue, but to have little effect on uptake into skeletal muscle (Wilkes et al., 2005). Whilst the contribution of the individual mechanisms of action reviewed is uncertain, it seems likely that topiramate-induced weight loss is multifactorial.

Topiramate has been the subject of a number of clinical trials to assess utility for the treatment of obesity. A meta-analysis of these trials

concluded that doses of between 96 and 196 mg for 24 weeks lead to a 6.5% additional weight loss compared to placebo-treated controls (Li et al., 2005) fully meeting FDA and EMA guidelines for weight loss. Adverse events recorded were paresthesia, altered taste (consistent with carbonic anhydrase inhibition as reviewed above), dizziness, memory impairment, insomnia and somnolence (Rosenstock et al., 2007). The intensity of these CNS dulling effects of topiramate are considered sufficient to preclude widespread use as a monotherapy (Bray et al., 2003) and may lead to depression (Wilding et al., 2004; Kalinin, 2007). Topiramate is also associated with teratogenicity (Hunt et al., 2009).

9. Cannabinoid targets and their receptors

Cannabinoid receptors are a class of G-protein linked cell membrane-expressed receptors with a typical 7 transmembrane domain structure. Two subtypes have been classified to date. The CB_1 receptor is the most widely expressed receptor in the central nervous system, but is also found peripherally in the lungs, liver and kidneys, gastrointestinal tract, testes and ovaries and in the cardiovascular system (Howlett et al., 2002; Di Marzo, 2009). In contrast the CB_2 receptor, which is 44% homologous with the CB_1 receptor subtype, is expressed in the cells of the immune system such as macrophages, B- and hematopoietic cells (Di Marzo, 2009) although there is some evidence of limited central expression (Onaivi, 2009). Cannabinoid receptors are activated by a family of locally synthesised endogenous lipids termed endocannabinoids. Two principal endocannabinoids that interact with CB_1 and CB_2 receptors have now been characterised: arachidonoyl ethanolamide (anandamide) and 2-arachidonoyl glycerol (2-AG). Both fulfil the necessary criteria for classification as neuromodulators. They are synthesised from arachidonic acid through distinct biosynthetic routes, are released from neurons in response to membrane depolarisation, have specific reuptake mechanisms and are inactivated by fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MGlipase) respectively. Plant cannabinoids such as THC also interact with the receptors (Di Marzo, 2009).

CB_1 receptors can act as a form of negative feedback control to the release of neurotransmiters such as GABA, which exerts an inhibitory tone or the excitatory amino acid, glutamate. In this process, activation of neurons by these agents leads to the de novo synthesis of endocannabinoids which are then released back across the synaptic left to inhibit further release. In this way, CB_1 receptor activation can cause have excitatory or inhibitory actions (Di Marzo, 2009).

10. Cannabinoids in the treatment of obesity

A substantial volume of preclinical data supports the hypothesis that CB_1 receptor antagonists have potential utility for the treatment of obesity (Kirkham and Williams, 2001). Levels of endocannabinoids increase in the hypothalamus and limbic area of the brain including nucleus accumbens during food deprivation and are reduced by feeding (Kirkham et al., 2002). Furthermore, hyperphagia driven genetically obese rodent strains such as the fa/fa Zucker rat, ob/ob and db/db mice have elevated hypothalamic endocannabinoid levels (see Vickers and Kennett, 2005). Null mice lacking the CB_1 receptor are lean, hypophagic, and are resistant to high fat diet-induced obesity (Cota et al., 2009; Ravinet Trillou et al., 2004). Consistent with the phenotype of the CB_1 knockout mouse, robust increases in food intake are widely reported after acute systemic administration of anandamide, 2-AG, *Cannabis sativa* (marijuana), or its principal ingredient the $CB_{1/2}$ receptor agonist, Δ^9-THC, in a number of animal species including man (e.g. Hollister, 1971; Foltin et al., 1988; Williams et al., 1998; Williams and Kirkham, 1999). This increase in food consumption is blocked by pretreatment with the selective CB_1 receptor antagonist, rimonabant but not by the selective CB_2 receptor antagonist, SR-144528 (Williams et al., 1998; Williams and Kirkham, 1999; Kirkham and Williams, 2001). Importantly, acute and chronic treatment with the prototypical CB_1 receptor antagonist, rimonabant, reduced both food intake and body weight in rodent studies and in man (see Vickers and Kennett, 2005).

The mode of action of CB_1 antagonists may be a summation of several different mechanisms. Cannabinoids may affect the desire to eat (i.e. the system that modulates the anticipation of food). This is likely to be predominantly a centrally mediated action as anandamide injection into the ventromedial hypothalamus increased food intake (Verty et al., 2005) as did direct injection of 2AG into the nucleus accumbens shell (Kirkham et al., 2002). In both cases, the endocannabinoid actions were antagonised by rimonabant pretreatment (see Vickers and Kennett, 2005). Consistent with the importance of the nucleus accumbens to reward function, rimonabant is reported to preferentially affect appetite for sweet foods in both rats and primates (Arnone et al., 1997; Simiand et al., 1998; Perio et al., 2001). Indeed, it is hypothesized that cannabinoid CB_1 receptor agonists induce over consumption of food by enhancing orosensory reward, or palatability, and that CB_1 receptor antagonists diminish the hedonic value of foods (Kirkham and Williams, 2001). An interaction between cannabinoids and the reward system may also account for the ability of CB_1 antagonists to influence responses to drugs of abuse such as nicotine (Wiskerke et al., 2008) and cocaine (Li et al., 2009). However, the relevance of an interaction between CB_1 antagonists and reward has been challenged by the failure of ICV administration of either a neutral CB_1 antagonist or inverse agonist to affect food-reinforced behaviour in rats (Sink et al., 2009). Finally it has been proposed that CB_1 receptor antagonists may, at least in part, cause weight loss by metabolic factors such as increasing energy expenditure (Bensaid et al., 2003; Poirier et al., 2005, Liu et al., 2005) and/or lipid metabolism (Cota et al., 2009) and this has been confirmed in clinical studies with the CB_1 receptor antagonist/inverse agonist, taranabant (Addy et al., 2008).

10.1. Rimonabant

Such findings suggested that CB_1 receptor antagonists could treat obesity through a mechanism that would be complementary to existing forms of drug therapy. Accordingly, rimonabant was progressed into Phase III trials by Sanofi-Synthelabo and significant reductions in body were reported in 1 and 2-year trials with >1000 patients in each (Van Gaal et al., 2008). A meta-analysis of weight loss in studies over 1 year of rimonabant 20 mg reported a baseline adjusted weight loss of 4.9 kg in obese subjects during double-blind placebo-controlled trials (Van Gaal et al., 2008) and 4.7 kg when trials of both obese and diabetic patients were included (Christensen et al., 2007). In addition 51% of treated patients achieved >5% weight loss compared to 19% of placebo controls. Thus, rimonabant fulfils current FDA criteria for weight loss. Significant improvements in plasma triglycerides, HDL cholesterol, fasting insulin and HbA1C were reported. Consistent with the reported peripheral metabolic effects of rimonabant, roughly half of the effects of rimonabant on lipid profiles and diabetic parameters may be independent of weight loss (Van Gaal et al., 2008). However, concern was expressed at the high drop-out rate from these studies (43% in pooled obesity trials) (Van Gaal et al., 2008) suggesting a lack of tolerability. While the most frequent side effects were GI disorders (30%), nausea (11.9%) and vomiting (3.9%), the high level of psychiatric side effects such as anxiety (5.5%), depressive symptoms or mood alterations with depressive symptoms (8.0%) and the possibility that these could lead to suicidal ideation was an issue of major concern to the regulatory authorities, especially as patients with any history of psychiatric disorder had been excluded from the trials. The risk of depressive symptoms was estimated at 2.5 fold higher than in placebo-treated patients by Christensen et al. (2007). As a consequence of this risk, the FDA refused marketing authorisation for rimonabant. Subsequently, in November 2008, the EMA withdrew its authorisation for rimonabant in Europe. The EMA stated that there was no clear way of minimising the risk to patients and indeed, that

the incidence of depressive symptoms had proved higher in clinical use than observed in trials. In addition, the EMA noted that the efficacy of rimonabant in clinical use was markedly less than in the clinical trial reports due to shorter periods of treatment (EMA, 2008).

10.2. Taranabant and Otenabant (CP-945,598)

Taranabant, a second CB_1 antagonist/inverse agonist has also been assessed in large scale clinical trials over a 52 week period. As for rimonabant, psychiatric side effects were observed in all studies (Addy et al., 2008, Aronne et al., 2010a; Kipnes et al., 2010; Proietto et al., 2010). Indeed, in the 2 year study of overweight and obese patients of Aronne et al. (2010a), a decision was taken to abandon the top two doses used (4 and 6 mg) in favour of the better tolerated 2 mg dose. Despite taking these steps, psychiatric side effects (as well as GI and other adverse events reported from the trials with rimonabant) were still an issue. Efficacy was similar to that of rimonabant and the 2 mg dose of taranabant achieved a 4 kg placebo-adjusted weight loss in the Aronne et al (2010a) study. Similar efficacy and side effects were observed in a second study with Taranabant using the 2 mg dose (Proietto et al., 2010). In a parallel study of obese patients with type 2 diabetes, a patient population that proved less susceptible to rimonabant-induced weight loss (Van Gaal et al., 2008), the 2 mg dose only achieved a 2.9 kg weight reduction over 1 year, while HbA1C was decreased by 0.61% compared to placebo (Kipnes et al., 2010). It was concluded that the cost benefit ratio was insufficiently high to warrant further development which was therefore halted (Kipnes et al., 2010). For this reason, psychiatric side effects are considered a class issue for first generation CB_1 antagonists. As a consequence, the development of other first generation CB_1 antagonists has also halted including the Pfizer CB_1 antagonist, Otenabant (CP-945,598) and the Bristol Myers Squibb compound, SLV-319.

10.3. TM38837

Several approaches to overcoming these issues have been proposed. Non-brain penetrant CB_1 antagonists might achieve weight loss by increasing metabolic rate and β-oxidation of lipids and via peripheral hypophagic mechanisms as proposed by Gomez et al. (2002). This approach has been pursued by 7TM Pharma whose TM38837 has successfully completed a Phase 1 clinical study (7TM Pharma Press Release, 2010). However, it remains to be shown that meaningful weight loss efficacy will be achieved without the central appetite suppressant effects of brain penetrant CB_1 antagonists or indeed that brain penetration of what has proven a necessarily lipophilic class of compounds will be prevented over long term administration.

An alternative approach has sought to develop neutral CB_1 receptor antagonists such as O-2050 (Gardner and Mallet, 2006), LH21 (Pavon et al., 2006) and AM4113 (Salamone et al., 2007). These differ from first generation CB_1 antagonists whose inverse agonist profiles in at least some in vitro screens (Maclennan et al., 1998; Mato et al., 2002) are hypothesised to mediate psychiatric and other side effects. While O-2050 elicited profound sedation in vivo (Gardner and Mallet, 2006), and the in vitro profile of LH21 is unclear (Jagerovic et al., 2004), AM4113 elicits hypophagia and weight loss in rats in a behaviourally specific manner (Salamone et al., 2007) and may have a reduced propensity to elicit psychiatric side effects (Sink et al., 2010a,b) or nausea (Chambers et al., 2007) in animal models.

11. Combination therapies for the treatment of obesity

It is clear that the control of food intake and body weight is modulated by multiple mechanisms. This may allow homeostatic responses to counter the effects of modulating any one of these mechanisms. Indeed, existing single mechanism approaches to obesity have rarely achieved greater than 5% weight loss over a 24–52 week period. This contrasts unfavourably with the >10% weight loss in completers over 3 years and 16% over 1 year obtained with the now withdrawn combination therapy of phentermine + fenfluramine ("phen–fen") in diet-restricted, lifestyle-modified individuals (Atkinson et al., 1997). A second study confirmed the efficacy of the combination over 34 weeks reporting a 10% (9.6 kg) placebo-adjusted weight loss in completers (Weintraub et al., 1992). Reports of the efficacy of the "phen–fen" combination may however be overstated as in both Atkinson et al. (1997) and Weintraub et al. (1992), the figures resulted from a completer analysis rather than an LOCF approach. Furthermore, the study of Atkinson et al. (1997) was not placebo-controlled. Nevertheless, largely on the basis of this data, it has been hypothesised that treatments that target two or more mechanisms of energy balance, might prove better weight loss therapies than those that exploit only a single mechanism. It has also been supposed that a combination of two or more commonly prescribed drugs targeting different mechanisms might have a better safety profile. The rationale behind this supposition relies on two issues. Firstly, the compounds chosen for use in a combination therapy will already have been established as well tolerated and secondly, their safety ratios can be further extended by use of lower doses should the combination therapy prove either additive or synergistic. On this basis, a number of combination therapies which exploit known weight loss mechanisms have recently been assessed in clinical trials. These include pramlintide + metreleptin; contrave, a combination of bupropion and naltrexone; empatic, a combination of bupropion and zonisamide; and qnexa, a combination of phentermine and topiramate. All four have generated interesting degrees of weight loss in trials to date.

11.1. Pramlintide + metreleptin

Recently, there has been considerable interest in the possibility of combining pramlintide with leptin to treat obesity. Initially there had been great hopes that leptin monotherapy would be useful, given the magnitude of the obesity syndrome associated with loss of either leptin or leptin receptor function. However a series of clinical trials failed to demonstrate any benefit of treatment with recombinant human recombinant human leptin (R-metHuLeptin; metreleptin). These failures resulted because of the development of leptin resistance as a consequence of obesity, which may be especially severe in the arcuate nucleus of the hypothalamus, an important site of action for the effects of leptin on feeding behaviour (Myers et al., 2008). A number of rodent studies, including one exploring different doses of pramlintide and leptin in a factorial design (Trevaskis et al., 2008), clearly demonstrated a synergistic effect which was attributed to amylin receptor stimulation reversing leptin resistance.

Similar results have now been obtained with human participants. In a proof of concept study, 177 human participants were randomised to pramlintide, metreleptin, or the combination, for 20 weeks, following a pretreatment period of 4 weeks with pramlintide (Roth et al., 2008, Ravussin et al., 2009). Those in the combination therapy group lost 10.2 kg (10.7%) more weight (after the pretreatment period) compared with either pramlintide (7.9 kg) or metreleptin (8.2 kg) alone. The unexpected effectiveness of metreleptin alone was attributed to the lasting effects of pretreatment with pramlintide (Ravussin et al., 2009). The placebo-adjusted efficacy of the combination therapy is however unclear, as no placebo-treated group was included in the study. It is therefore possible that the severe 40% caloric deficit diet, that all participants in the trial underwent, might alone have been responsible for substantial weight loss. It should also be noted that the single dose combination used in this study was not optimised and may not have revealed the full potential of the treatment. Finally, it is of interest, given the need for the trial participants to administer the treatments to themselves twice daily by subcutaneous injection, that the drop-out rate at the end of 20 weeks was only 32%. The most common source of adverse events was the injection site. Indeed, in previous trials where

peptides have been injected over long periods of time, immunogenicity has been a problem giving rise to painful local inflammation at the site of injection. Nevertheless adverse events at the site of injection of subjects administered pramlintide + metreleptin appear to have been modest. Consistent with this, there was no evidence of loss of efficacy at the end of the 20 week dosing period and hence no evidence of immune-related tolerance (Ravussin et al., 2009). These results may therefore suggest that self-injected of treatments can be tolerated outside of the diabetic population and would not be an obstacle to gaining acceptance in the market. Additional support to the use of pramlintide as one component of a combination therapy has been provided by a study in which it was co-administered with either sibutramine or phentermine and led to weight loss of 11.1% and 11.3% respectively after 24 weeks (Aronne et al., 2010b).

11.2. Contrave

Contrave is a fixed dose combination therapy for obesity in a single tablet consisting of sustained release (SR) formulations of both naltrexone and bupropion (Orexigen Therapeutics Inc press release may 22nd, 2007). The mechanisms upon which these treatments act both modulate the firing of POMC neurons in the arcuate nucleus of the hypothalamus. Bupropion, a dopamine and noradrenaline reuptake inhibitor stimulates POMC firing (Pelletier 1993; Greenway et al., 2009a) and hence may suppress appetite by the release of αMSH. POMC neuronal stimulation however, also results in the release of β-endorphin which is thought to act as a negative feedback control on POMC firing (Cone, 2005). The existence of such negative feedback control systems has been hypothesised to at least partially account for the early plateau in weight loss efficacy and hence relatively poor efficacy of bupropion in the two clinical studies for weight loss conducted to date (Anderson et al., 2002; Jain et al., 2002; Greenway et al., 2009a).

This hypothesis was tested by assessing the effects of a combination of bupropion and the μ-opiate antagonist, naltrexone on food intake in overnight food-deprived lean or DIO C57Bl/6J mice (Greenway et al., 2009a). In both cases, the combination elicited more marked reductions in food intake over a 1 h period than was observed with either component alone at the doses selected. However, in neither case could evidence for a synergistic rather than an additive effect be proven. It could also not be demonstrated that the effect of the combined treatment on POMC neuronal firing in mice was more effective that individual components. No chronic studies with the combination treatment have been published and it is not clear if naltrexone affects the metabolism of bupropion or visa versa. In addition to its possible effects on POMC neuronal firing, naltrexone may act to reduce the rewarding properties of food (Yeomans and Gray, 2002), either through direct actions on mesolimbic dopamine reward pathways (Gianoulakis 2009), or via a specific pathway that allows food-elicited opiate release in the hypothalamus to modulate mesolimbic reward systems (Rada et al., 2010). Notwithstanding the existence of these mechanisms and evidence that acutely administered opiate antagonists reduce food intake in both animals and man, naltrexone alone has had little effect on weight loss in clinical trials to date (Atkinson et al., 1985; Malcolm et al., 1985).

Despite the lack of clear evidence that naltrexone and bupropion would have a synergistic effect on food intake, a clinical proof of concept study with 238 obese subjects with a BMI averaging 35 kg/m^2 was initiated (Greenway et al., 2009a). There was no run in period and dietary restriction was not implemented thereby favouring apparent weight loss. After 16 weeks of treatment, the average weight loss of the combination therapy (bupropion SR 300 mg + naltrexone 50 mg immediate release) was 3.7 kg compared with 3.2 kg for bupropion alone, 1.7 kg for naloxone alone and 0.6 kg for placebo using an ITT group LOCF treatment approach. The percentage of patients achieving >5% weight loss for the combination treatment was 32% vs 26% for bupropion alone, 15% for naltrexone alone and 12% for placebo. At this point, after 16 weeks of administration, there was no evidence for a synergism between the two treatments. After 24 weeks however, the combination treatment weight loss had reached 4.4 kg, compared with 3.1 kg for bupropion alone, suggesting that over a longer time period the treatment effects had diverged, although, the absence of 24 week naltrexone alone and placebo-treated groups, prevents firmer conclusions being drawn. The main side effect issues were nausea (31%), headache (15.7%), dizziness (9.1%) and insomnia (13.4%). 17.6% of subjects on the combined treatment left the trial due to adverse events compared to 9.1% of placebo controls, but there were no significant drug related adverse events suggesting that the combination was well tolerated (Greenway et al., 2009a).

Subsequently, a larger double-blind placebo-controlled study was conducted in 419 diet-restricted obese subjects with a BMI of between 30 and 40 kg/m2 over 24 weeks which assessed the effect of naltrexone 48 mg alone or bupropion SR 400 mg when combined with placebo or one of three doses of naltrexone 16, 32 or 48 mg/kg (Greenway et al., 2009b). Using analysis of the ITT population with a LOCF approach, naltrexone alone was not found to elicit a significant weight loss (1.1 kg vs 0.9 kg for placebo). Bupropion also had a relatively modest effect alone of 2.6 kg. When combined with naltrexone 16, 32 or 48 mg, however, significant weight loss of 5.1, 5.1 and 4.0 kg respectively was observed. The bupropion and bupropion + naltrexone combination were continued for 48 weeks, while placebo treatment was halted. At the end of this time, weight loss in the bupropion alone group was 2.7 kg vs 7.4, 8.2 and 10.0 when combined with 16, 32 or 48 mg of naltrexone respectively. These data endorsed the hypothesis that naltrexone and bupropion can act synergistically to elicit weight loss in man. Indeed, 50% of participants achieved >5% weight loss on the bupropion + naltrexone 16 mg combination and 51% with the 32 mg naltrexone dose. The corresponding figures for achieving >10% weight loss were 22 and 25% respectively. Amongst study completers >5% weight loss was achieved by 72 and 68% respectively while >10% weight loss was achieved by 34 and 32% respectively. These data easily exceed both the FDA and EMA criteria for a weight loss agent. Nausea, vomiting, dizziness and headache were the predominant side effects and these accounted for a far higher drop-out rate amongst the bupropion + naltrexone 48 mg (62.5%) group than when given 32 mg (21%) or 16 mg (33%).

The results of this latter study were used to select a dose of 32 mg naltrexone for two 56 week double-blind placebo-controlled Phase III studies, COR-I and COR-II. Both studies were conducted in obese and overweight subjects with a 1 month run in period. COR-1 was designed to study two dose combinations of contrave given twice daily in 471 treated vs 511 placebo-treated controls, while COR-II evaluated a single dose given twice daily in 702 subjects undergoing an intense behavioural modification program. In both cases, a sustained release formulation of naltrexone was substituted for the previously utilised immediate release form of the drug. Analyses of the ITT population utilising an LOCF approach indicated that >10% weight loss was achieved by 24.6% vs 7.4% of controls in COR-I, while in the COR-II study, 32.9% achieved >10% weight loss vs 5.7% of controls. >15% weight loss was achieved by 11.9% vs 2% of controls in COR-I and 15.7% vs 2.4% of controls in COR-II. While these are encouraging data that suggest the treatment will readily exceed regulatory criteria, the key figures relating to the overall weight loss and proportion that achieved >5% weight loss vs placebo have, however, not yet been revealed.

A third 56 week Phase III double-blind study (Orexigen Press release, June 25th, 2010) was conducted in 505 overweight or obese patients with type 2 diabetes, whose HbA1C scores averaged 8% and who were maintained to concurrent anti-diabetic medication. Average weight loss has not been disclosed at the time of writing, but 44.5% of subjects lost over 5% body weight compared with 18.9% of placebo. Significant placebo-adjusted reductions in HbA1C levels of 0.5% were observed (0.6% in patients with starting HbA1C levels >8% at initiation of treatment). Placebo-adjusted reductions in hyperinsulinaemia (−3.1%) and hyperglycaemia (−7.9 mg/dl) were also observed.

In addition to significant weight loss and reduced HbA1C, all studies also reported improvements in cardiometabolic indices with reduced fasting plasma triglycerides and low density lipoproteins and increased high density lipoprotein. As for the Greenway et al. (2009b) Phase IIb study, the principal side effects experienced in the COR-I and -II studies were nausea, vomiting and dizziness (Orexigen Therapeutics Inc Press release Oct 27th 2009, June 25th, 2010). These beneficial effects of contrave, have not apparently translated into improved overall cardiovascular function, as, while placebo-treated patients were observed to have lost an average of 2 mm Hg, those on contrave did not, and exhibited a 1 bpm increase in heart rate (Orexigen press release, June 26th, 2010) with one report of palpitations in the trials reported to date. Despite evidence that bupropion may cause seizures or depressed mood and suicidality in man or adolescents when overdosed (Spiller et al., 1994; Ayers and Tobias, 2001), no such events have been observed in the clinical studies reported (Orexigen Therapeutics Inc press releases June 6th and Oct 27th 2009). In the COR-1 and -II studies, drop-out rates were 25.9% (of which 4.6% were due to nausea) compared to 13% in controls (Orexigen Therapeutics Inc press release June 6th 2009). Headache, dizziness, and vomiting also contributed to discontinuation, although, it is reported that these are generally mild to moderate and tolerated after the first weeks of treatment (Orexigen Theapeutics press report June 26th, 2010). In light of the regulatory authorities recent concerns regarding psychiatric side effect issues and the known propensity for bupropion to elicit depressed mood, a specific 24 week Phase III trial was conducted in obese and overweight patients with major depressive illness. This concluded that contrave significantly ameliorated depressive symptoms as scored by the MADRS (Orexigen press release June 26th, 2010). Contrave is due to be reviewed by an FDA advisory panel on December 7th 2010.

11.3. Qnexa

Qnexa is a combination therapy consisting of low doses of the amphetamine, phentermine and a sustained release formulation of the anticonvulsant topiramate.

Studies in the public domain on the possible synergy between topiramate and phentermine are almost exclusively clinical. Three Phase III studies have now been completed using three possible dose combinations of phentermine and topirimate (SR): low dose 3.75 mg phentermine/23 mg topiramate (SR), mid dose 7.5/46 and full dose 15/92. The full dose combination represents the bottom end of the range of doses of phentermine (15–32 mg) and topiramate (96–196 mg) that have been used as monotherapy (Table 1).

The first "Equate" trial assessed the effect of mid and full dose combinations in 756 lifestyle-modified and diet-restricted obese patients with a mean BMI of 36.3 kg/m^2. The double-blind, placebo-controlled study was run over a 28 week period, 4 of which were used for dose titration and included groups given topiramate or phentermine alone. Using an ITT LOCF analysis, mid dose and full dose Qnexa was associated with an impressive weight loss of 8.3 and 9.0 kg respectively, representing 8.5% and 9.2% of body weight. Placebo controls lost 1.5 kg (1.7%) over the same period. 66% of subjects on full dose Qnexa achieved ≥5% and 41%>10% body weight loss. In contrast, 15% of placebo controls achieved 5% weight loss and 7% achieved ≥10% (Vivus Inc press release, Dec 11th 2008).

A second double-blind placebo-controlled trial, "Equip", examined 1267 morbidly obese patients with a mean BMI of 42.1 kg/m^2 over 56 weeks, 4 of which were used for dose titration. Following the titration period, patients were treated once daily with low or full dose Qnexa or placebo. Using an ITT LOCF analysis, placebo, low and high dose, Qnexa achieved 1.9 kg (1.6%), 5.9 kg (5.1%) and 12.8 kg (11.0%) body weight loss respectively. Furthermore, 67% of full dose qnexa treated participants achieved >5% body weight loss compared with 17% of controls. Completion rates for the study were 47%, 57% and 59% respectively and significant improvements in blood pressure, plasma triglycerides and cholesterol were claimed (Vivus Inc press release, September 9th, 2009).

A third study, "Conquer", examined the effects of placebo and mid or full dose Qnexa on 2487 lifestyle-modified and diet-restricted obese subjects with a mean BMI of 36.3 kg m^2 with co-morbidities (high blood pressure, high cholesterol or diabetes) over 56 weeks (initial 4 weeks for drug titration). Weight loss at the end of this time was comparable to that seen in the "Equip" trial with full dose Qnexa eliciting 10.7 kg (10.4%), mid dose 8.6 kg (8.4%) weight loss compared with 1.8 kg (1.8%) in the placebo group. 70% of full dose and 62% of mid dose patients achieved ≥5% weight loss compared to 21% of controls. Qnexa-induced weight loss was associated with significant weight loss-dependent reductions in blood pressure. Indeed, in the Conquer trial, >5%, >10% or >15% body weight in the Conquer trial was associated with reductions in both systolic (−4.8, −7.4 and −9.4 mm Hg) and diastolic (−3.8, −5.0, and −5.8 mm Hg) blood pressure respectively. However, the highest dose combination was also associated with an increased heart rate of 1.5 bpm. This was not seen with the mid dose combination which was associated with an overall −3.61/1.76 (systolic/diastolic) mm HG over 28 weeks.

Other cardiometabolic indices were also improved such as triglycerides and HbA1C values, the latter despite maintained antidiabetic treatment. Also in a separate Phase II study of patients with obstructive sleep apneas, the apnea/hypoxia index was significantly improved with beneficial effects on overnight blood oxygen levels and respiratory disturbances (Vivus press release June 8th, 2010).

Overall in Phase III studies to date, completion rates were 57%, 69% and 64% for placebo, mid and full dose Qnexa respectively (Vivus Inc press release, September 9th, 2009) suggesting reasonable tolerability. In all studies, similar adverse events were noted consisting of dry mouth, paresthesia, constipation, altered taste and insomnia. Following the psychiatric issues that led to the FDAs rejection of the CB_1 antagonist, rimonabant, in 2007 (Christensen et al., 2007) and the known propensity of topiramate to cause depression and nervousness (Wilding et al., 2004; Kalinin, 2007), psychiatric mood assessments were made monthly and these showed no evidence of increased overall depressed mood or suicidality (Vivus Inc press release, September 9th, 2009). In addition, as topiramate monotherapy can cause cognitive dysfunction (Wilding et al., 2004), the Equip and Conquer trials made a detailed report of discontinuation rates for cognitive events. The rate of discontinuation for those patients on the high dose combination of qnexa was 0.9%, mainly due to disturbances in attention, amnesia and memory impairment (Vivus press release October 29th 2009). This compares favourably with the 3–4% discontinuation rate associated with topiramate monotherapy (Wilding et al., 2004).

Despite the apparently relatively benign safety profile of qnexa, the compound was not recommended for approval by an FDA expert panel on July 15th, 2010. One issue raised was the occurrence of psychiatric events where it was revealed that the rate of withdrawal of patients on the highest dose for depression, anxiety and sleep disorders was 7 fold higher than in placebo. This finding may have been masked in previous reports grouping all qnexa dose levels together. In addition, the committee were unhappy with the risk of cognitive dysfunction and with the increase in heart rate, although this could be avoided by adopting the almost equally efficacious mid dose. Finally, the FDA panel were particularly concerned about the teratogenic potential of the qnexa due to both its topirimate content (Hunt et al., 2009) and its teratogenic effects at high doses in preclinical studies. To counter this risk, Vivus proposed labelling against use in pregnant women, but this step was deemed inadequate to protect women of childbearing age using the drug.

It was concluded that while Qnexa is capable of eliciting strikingly significant weight loss that readily meet both FDA and EMA regulatory requirements for efficacy, with study completers over 56 weeks achieving an approximately 14% body weight loss of whom around 85%

achieved >5% body weight loss, insufficient data had been presented to assure a satisfactory risk benefit ratio at present, particularly where treatment was for more than a year.

11.4. Empatic

Empatic is another combination therapy, in this case utilising the anorexic properties of sustained release formulations of both bupropion and zonisamide. It was hypothesised that bupropion might offset the depressive and sedative issues associated with zonisamide, while the latter might reduce the likelihood of bupropion-induced seizures (Gadde et al., 2007). A pilot clinical study of 18 diet-restricted obese women with a mean BMI of 36.8 kg/m^2 was conducted over 12 weeks where subjects were treated with either zonisamide immediate release (IR) alone or a combination of zonisamide (IR) 100 mg rising to 400 mg over 4 weeks and bupropion (IR) 100 mg, rising to 200 mg after 2 weeks. There was no placebo-treated group in this study. Using an ITT LOCF analysis, recorded body weight loss was 2.9 kg (3.1%) in the zonisamide alone group compared to 7.2 kg (7.5%) in the combination therapy group. Sixty six percent of the subjects receiving the combination lost >5% body weight compared with 22% on zonisamide alone (Gadde et al., 2007). Zonisamide alone was relatively poorly tolerated with 44% leaving the trial due to fatigue, language and speech difficulties, drowsiness, nausea or diarrhoea, while the combination was also better tolerated with a 22% drop-out rate. Despite the omission of a placebo group, the trial was adequately constructed to provide evidence that the two treatments could elicit at least an additive effect on body weight loss.

A subsequent Phase 2b trial of the empatic concept used two doses of zonisamide (SR) 120 and 360 mg alone, the same doses combined with bupropion (SR) 360 mg together with additional placebo and bupropion SR monotherapy controls (Orexigen Pharmaceuticals Inc, press release, Sept 30, 2009). The double-blind placebo-controlled trial was conducted over 24 weeks in 729 obese subjects (BMI 30–45 kg/m^2) subjected to a restricted diet and exercise regime. Headline results only have been revealed to date using an ITT LOCF approach. Empatic containing 120 mg zonisamide resulted in a 6.1% weight loss, while the 360 mg zonisamide containing dose gave a 7.5% weight loss. Both doses gave significantly greater weight loss when compared with the placebo-treated controls. Zonisamide 120 mg and 360 mg alone gave 3.2 and 5.3% weight loss while bupropion 360 mg gave a 2.3% weight loss and placebo a 1.4% weight loss. 60.4% of high dose empatic and 46.9% of lower dose empatic-treated participants achieved >5% weight loss and the corresponding figures for >10% weight loss were 32.3 and 24.7% respectively. Empatic-induced weight loss was progressive and had not reached a plateau at the end of the study. Furthermore, improvements in key metabolic indices such as plasma triglycerides, blood pressure and fasting insulin levels were claimed. Discontinuation rates were 34% for high dose empatic vs 29% for placebo. Main adverse events were headache, insomnia and nausea, while urticaria (hives) also contributed to discontinuation. These results suggest that empatic can elicit clinically meaningful weight loss, but a more detailed results analysis is required before firm conclusions can be drawn. It should be noted that the recent FDA review of qnexa focussed on issues derived from the presence of topiramate, Many of the same concerns could apply to empatic as the zonisamide component has been associated with cognitive impairment (Mula and Sander, 2007), mood disorders (Mula and Sander, 2007) and possibly teratogenicity (Ohtahara and Yamatogi, 2004).

12. Conclusions

The most efficacious currently available treatment for obesity, sibutramine, is able to elicit an average body weight loss of 4.45 kg over a 52 week period (Li et al., 2005) but is no longer available in Europe. Of the various treatments in late stage clinical trials, qnexa and tesofensine, appear to offer the most significant improvements in efficacy over sibutramine (Table 3). Of these, qnexa appears to be the most efficacious, with the highest dose achieving an average of 10 kg (9%) placebo-adjusted weight loss over 52 weeks with over 60% of participants losing over 10% of their weight following an LOCF analysis. The figures for those who completed the trial are correspondingly higher and the reported significant improvement in blood pressure appears to dispel any fears that the hypertensive effects of the phentermine component, the dose of which is within the range used as monotherapy, might be manifested in the mixture, although it may be responsible for the increase in heart rate (1.5 bpm) observed and this might necessitate use of the almost as efficacious mid dose, rather than the high dose. However, the main issues for qnexa such as cognitive dysfunction, psychiatric events and teratogenicity originate from the topiramate content. The recent FDA review focused on these issues and requested further proof of safety exceeding the 1 year duration studies that had been conducted to date. Providing such data for either qnexa or any future submissions is likely to prove a significant financial hurdle with no guarantee of a successful outcome.

Tesofensine 0.5 mg also looks promising, matching the average weight loss achieved by qnexa with what appears to be excellent tolerability since only 16% of participants discontinued from receiving the treatment over 24 weeks. However, the 0.5 mg dose level of tesofensine produced overt increases in heart rate, if not blood pressure. If confirmed in the forthcoming Phase III trials, it may be necessary to improve the safety margin by adopting the far less efficacious 0.25 mg dose.

The exenatide + metreleptin proof of concept study is of considerable interest as the non-optimised dose combination reduced body weight by 10.7% with 58% of subjects achieving >10% weight loss. The relatively low drop-out rate (32%) attests to the viability of self-injected treatments in a motivated patient population. Despite these encouraging data, the value of this approach awaits results from more definitive trials with an optimised dose combination and the inclusion of a placebo control.

Contrave and empatic have similar but more modest efficacy than either qnexa or tesofensine with 25–30% of patients achieving >10% weight loss and a mean weight loss in the range of 5–6.5 kg. Nevertheless, if this degree of weight loss were maintained in subsequent trials, it would still represent a distinct improvement over sibutramine, the most efficacious currently marketed treatment, without its cardiovascular liabilities and should be sufficient to have a clinically meaningful impact on obesity co-morbidities (Goldstein 1992; Knowler et al., 2002). However, one of the components of empatic is the anticonvulsant, zonisamide, which has a very similar adverse event profile to topiramate. A note of caution should also be expressed regarding the cardiovascular profile of contrave, where the anticipated benefits of weight loss on cardiovascular function have not been observed to date and, indeed, when compared to placebo, a small increased in both blood pressure and heart rate has been observed (Orexigen press release, June 26th, 2010). The full outcome of the trials conducted with these agents is not yet in the public domain, but reported tolerability, as judged by the 20–30% discontinuation rates over 24 weeks, looks promising.

The weight loss mediated by lorcaserin is also similar to current therapy and its tolerability appears unremarkable with 40–45% of patients discontinuing treatment over 52 weeks. Safety may however be a strong point of this approach as the principle concern regarding cardiovascular safety has been largely dispelled by the trials conducted to date over 2 years. Nevertheless, it should be noted that should the compound be marketed and a wider population of subjects exposed, any risk of valvulopathy will become apparent and this may still be an area of concern for regulatory bodies. Furthermore, while lorcaserin may be of use as monotherapy for the treatment of obesity, it is also conceivable that both its tolerability and efficacy might well be improved as part of a co-therapy approach.

In conclusion, a number of new approaches to the treatment of obesity are currently in late stage development and some appear, at present, to offer better efficacy and improved tolerability than current therapy.

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