Invited review

What is the prognosis for new centrally-acting anti-obesity drugs?

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1. Introduction

The accepted definition of obesity is a body mass index (BMI; weight in kg/height in m²) of greater than 30. According to the latest figures from IASO (International Association for the Study of Obesity) and IOTF (International Obesity Task Force), 475 million adults and up to 50 million children in the world are now obese (IOTF, 2010). Using data for England in 2008 as an example, ~25% of adult males and females were obese and ~30% of boys and girls (2–15 years of age) were either overweight (BMI = 25–30) or obese (Health Survey for England, 2008). If obesity in the UK continues to increase at its current rate, the UK Government estimates that 50–60% of British adults and 25% of children will be obese by 2050 (UK Government Foresight Report, 2007). The major contributors to the increased level and severity of obesity are easy access to a diet rich in fat, sugar and salt together with a much more sedentary lifestyle than in previous times (Prentice and Jebb, 1995; Deedwania, 2004). However, recent epidemiological data in children indicates that the amount of exercise taken has relatively little influence on the occurrence and degree of obesity (Metcalf et al., 2011), whereas there is a very strong association between daily calorie intake, consumption of "fast food" and obesity (Block et al., 2004; Bowman et al., 2004). Although unhealthy, Western, eating habits are believed to be a pivotal cause of obesity, the epidemic has become a global problem because of the rising popularity of a fast foods and a Western lifestyle in many developing nations (particularly in urban locations) (International Obesity Task Force [IOTF], 2010). Moreover, in many populations, e.g., Asians, the health risks occur at BMI values below the 25 cut-off for overweight, and at any given BMI above 25, Asians suffer a disproportionately greater burden of disease than Caucasians (World Health Organisation [WHO] Expert Consultation, 2004).

Obesity is not merely a cosmetic issue because it is causal factor in many serious diseases including dyslipidaemia, hypertension, stroke, myocardial infarction, Type 2 diabetes and some cancers (IASO, 2012). For this reason, the rapidly increasing level of obesity is likely to result in substantial health, financial and social burdens across the world unless effective interventions are employed. For many obese subjects, attempts to adhere to a healthy diet and lifestyle have not addressed this problem. In these cases...
supplementation with pharmacotherapy or bariatric surgery will be required.

In this review, we discuss the challenges for the development of centrally-acting anti-obesity drugs arising from a conservative regulatory environment, difficult marketing conditions and unrealistic patient expectations. We also critically assess the three drug candidates that are currently at the pre-registration phase in the USA and review a wide range of novel compounds and drug targets that are in discovery or early clinical development.

2. A brief history of centrally-acting anti-obesity

2.1. The first generation of weight-loss drugs

Anti-obesity drugs should be used only as an adjunct to first-line treatment for obesity treatment, which is a healthy diet, exercise and lifestyle modification. At present, there are no centrally-acting drugs which are on the market for the treatment of obesity in Europe (Table 1). In the USA, the only central nervous system (CNS) drugs that can be used to treat obesity are the sympathomimetic, appetite suppressants that are only approved as short-term (<12 weeks) treatments. These drugs have been marketed for many years and include phenetermine, phenidimetrazine, diethylpropion and benzphetamine. Fifty years ago, &-amphetamine (dextroamphetamine) and even methamphetamine were prescribed as appetite suppressants, but their frequent diversion and abuse led to them becoming highly restricted Controlled Drugs. In the 1990’s, the 5-HT releasing agents, fenfluramine and O-fenfluramine, were withdrawn from the market because their prolonged use was linked to life-threatening primary pulmonary hypertension and cardiac valvulopathy.

2.2. Sibutramine

Sibutramine, which is a centrally-acting noradrenaline/serotonin reuptakeinhibitor (Heal et al., 1998), is the most recent anti-obesity drug casualty. Results from large, Phase 4, cardiovascular outcome trial found sibutramine was linked to an increase in non-fatal heart attacks and strokes in subjects with pre-existing cardiovascular problems (James et al., 2010). For this reason, sibutramine was withdrawn from the European and North American markets in 2010.

2.3. Rimonabant

Rimonabant is a centrally-acting cannabinoid CB1 receptor inverse agonist. In pivotal Phase 3 clinical trials, rimonabant was shown to be efficacious in treating obesity with or without its associated comorbidities (Déspres et al., 2005; Van Gaal et al., 2005; Scheen et al., 2006; Pi-Sunyer et al., 2006) and it was approved as an anti-obesity drug by the European Medicines Agency (EMA) in 2006. However, later reports of severe depression and suicidal thoughts in patients taking rimonabant (Pi-Sunyer et al., 2006; Christensen et al., 2007) led to a recommendation for non-approval by the US Food and Drugs Administration (FDA) Advisory Committee that prompted Sanofi-Aventis to withdraw rimonabant’s licensing application in the USA. Although the drug remained on the European market for some while afterwards, an ever increasing number of reports of psychiatric adverse events associated with rimonabant use eventually led EMA to suspend the European marketing authorisation for rimonabant in 2008.

2.4. Other anti-obesity drugs

In the absence of any centrally-acting anti-obesity drugs in Europe, prescription pharmacotherapy in this indication is restricted to orlistat, which has a peripheral mechanism of action. Orlistat, an inhibitor of gastric and pancreatic lipases that blocks fat absorption from the gut (McNeely and Benfield, 1998), is approved as a prescription medicine in most countries around the world. This drug has recently been granted an “over the counter” licence (albeit at reduced strength) in Europe and the USA. Celtislat is a newer inhibitor of gastric and pancreatic lipases that is currently under development for the management of weight loss in obese patients with or without medical complications. Celtislat is reported to have fewer adverse side-effects than orlistat (Kopelman et al., 2007, 2010).

3. Late-stage, centrally-acting, anti-obesity drug candidates

In 2009–10, three new CNS medications for obesity were submitted to the Food and Drugs Administration (FDA) for regulatory evaluation, viz the 5-HT2C receptor agonist, lorcaserin (Lorqess®), and fixed-dose, drug combinations of phentermine + topiramate (Qnexa®) and bupropion + naltrexone (Contrave®).

3.1. Lorcaserin

The scientific rationale for the use of 5-HT2C agonists to treat obesity is based on the observation that the hypophagic effect of fenfluramine is believed mediated by indirect activation of these receptors (Lee et al., 2004; Vickers et al., 2001), and this finding prompted several companies to explore the development of 5-HT2C

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Table 1

<table>
<thead>
<tr>
<th>Drug</th>
<th>Trade name</th>
<th>Mode of action</th>
<th>Company</th>
<th>USA</th>
<th>European Union</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orlistat</td>
<td>Xenical</td>
<td>Lipase inhibitor</td>
<td>Roche</td>
<td>Marketed</td>
<td>Marketed</td>
</tr>
<tr>
<td>Orlistat</td>
<td>Alli (OTC)</td>
<td>Lipase inhibitor</td>
<td>Roche</td>
<td>Marketed</td>
<td>Marketed</td>
</tr>
<tr>
<td>Phentermine</td>
<td>Ionamin, Duromine</td>
<td>Noradrenaline (NA) + dopamine (DA) releasing agent</td>
<td>Generic</td>
<td>Marketed</td>
<td>Withdrawn in 2001</td>
</tr>
<tr>
<td>Methamphetamine*</td>
<td>Dexoxyn</td>
<td>DA + NA releasing agent</td>
<td>Generic</td>
<td>Marketed</td>
<td>Withdrawn in 2000</td>
</tr>
<tr>
<td>Phendimetrazine</td>
<td>Tepani, Bontril</td>
<td>Sympathomimetic</td>
<td>Generic</td>
<td>Marketed</td>
<td>Withdrawn in 2000</td>
</tr>
<tr>
<td>Diethylpropion</td>
<td>Tenuate, Apisate</td>
<td>Sympathomimetic</td>
<td>Generic</td>
<td>Marketed</td>
<td>Withdrawn in 2000</td>
</tr>
<tr>
<td>Benztropine</td>
<td>Didrex</td>
<td>Sympathomimetic</td>
<td>Generic</td>
<td>Marketed</td>
<td>Withdrawn in 2000</td>
</tr>
<tr>
<td>Sibutramine</td>
<td>Reductil, Meridia</td>
<td>Noradrenaline (NA) + 5-HT reuptake inhibitor</td>
<td>Abbott</td>
<td>Withdrawn in 2010</td>
<td>Withdrawn in 2010</td>
</tr>
<tr>
<td>Rimonabant</td>
<td>Appetia</td>
<td>Cannabinoid CB1 antagonist</td>
<td>Sandi-Aventis</td>
<td>Not approved</td>
<td>Non-Approval</td>
</tr>
<tr>
<td>Bupropion/naltrexone</td>
<td>Contrave</td>
<td>DA reuptake inhibitor/opioid antagonist</td>
<td>Orexigen/Takeda</td>
<td>Pre-registration</td>
<td>Phase 3</td>
</tr>
<tr>
<td>Topiramate/phentermine</td>
<td>Qnexa</td>
<td>Unknown/NA + DA releasing</td>
<td>Vivus</td>
<td>Pre-registration</td>
<td>Pre-registration</td>
</tr>
<tr>
<td>Lorcaserin (APD356)</td>
<td>Lorcass</td>
<td>5-HT2C agonist</td>
<td>Arena/Eisai</td>
<td>Pre-registration</td>
<td>Phase 3</td>
</tr>
<tr>
<td>Zonisamide + bupropion</td>
<td>Empatica</td>
<td>Unknown/DA reuptake inhibitor</td>
<td>Orexigen</td>
<td>Phase 2</td>
<td>Phase 2</td>
</tr>
</tbody>
</table>

OCT – Over the counter (non-prescription) medicine.
Sources: Medtrack® and information posted by companies, FDA and EMA on official websites.
* Approved only for the treatment of refractory obesity.

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agons as novel anti-obesity drugs. 5-HT₂C agonists to have undergone preclinical or clinical evaluation include Ro 60-0175, VR 1065, and VER-8775 (Vernalis/Roche), LY 448100 (Lilly) as well as lorcaserin (Arena Pharmaceuticals). Lorcaserin is a high affinity 5-HT₂C receptor full agonist (Ki: h5-HT₂C = 15 nM; r5-HT₂C = 29 nM) that is devoid of affinity for a wide panel of other G-protein coupled receptors (GPCRs) and ion channels (Thomsen et al., 2008). With respect to the 5-HT₂A and 5-HT₂B receptor subtypes, lorcaserin has selectivity ratios of ~15-fold and 100-fold, respectively (Thomsen et al., 2008). The benefits of lorcaserin have been evaluated in three, pivotal, Phase 3 clinical trials, i.e., two in obesity without major medical complications (so called “healthy obese” subjects) and one in overweight or obese adults with Type 2 diabetes. At Week-52, the placebo-subtracted weight-loss produced by lorcaserin was 3.6 kg (Smith et al., 2010) and 2.9 kg in healthy obese subjects (Lorcaserin NDA, 2010) and 3.1 kg in obese diabetics (Arena Pharmaceuticals Press Release, 2010) (Table 2). The corresponding responder analyses revealed that ≥5% weight-loss was achieved by 27.2% (Smith et al., 2010) and 22.2% (Fidler et al., 2011) in subjects with obesity and 21.4% in obesity with Type 2 diabetes (Arena Pharmaceuticals Press Release, 2010). In spite of the widespread belief that having a selective 5-HT₂C full agonist would increase efficacy, the weight-loss produced by lorcaserin was remarkably similar to the 3.5 kg weight-loss at 1-year that was reported for the indirect 5-HT₂C receptor agonist, n-fernfluamine (Guy-Grand et al., 1989). Lorcaserin’s clinical efficacy was described by the FDA as “minimal” in its non-approvable letter (Arena Pharmaceuticals Press Release, 2010). Lorcaserin’s ability to decrease weight is almost certainly inferior to rimonabant (Déspres et al., 2005; Van Gaal et al., 2005; Scheen et al., 2006; Pi-Sunyer et al., 2006) or sibutramine (Apfelbaum et al., 1999; James et al., 2000) which have been withdrawn from the market. The effect of lorcaserin on a range of cardiometabolic risk factors is reported in Table 2 and while many of the differences are highly significant when statistically analysed, their small size, which is consistent with the very modest degree of weight reduction, indicates they are likely to be of minimal clinical benefit.

As discussed earlier in this review, safety is of primary concern to the regulatory agencies. Common adverse events associated with lorcaserin use are consistent with its serotonergic mechanism of action, i.e., an increased incidence of blurred vision, dizziness, somnolence, headache, gastrointestinal disturbance and nausea (Smith et al., 2010; Fidler et al., 2011). Concern that lorcaserin’s serotonergic mechanism might cause cardiac valve damage appears to have been allayed by results from extensive echo-cardiographic monitoring throughout its clinical development. However, 5-HT₂A receptor agonists are hallucinogenic (Fiorella et al., 1995; Chojnacka-Wójcik and Kódzinska, 1997) and in a clinical trial in drug-experienced human volunteers the two highest doses of lorcaserin produced subjective effects of “floating”, “spaced out” and “euphoric mood” (Shram et al., 2010) leading the FDA to state that if the drug is approved lorcaserin will become a Schedule 4 Controlled Drug in the USA (Arena Pharmaceuticals Press Release, 2010). The other major safety concern highlighted by the FDA in its non-approvable letter was an increased incidence of mammary adenocarcinomas in female rats and brain astrocytomas in male rats. In January, 2012, Arena announced that it had prepared and submitted its responses to the FDA on safety concerns relating to lorcaserin with a view to resubmitting its NDA (Arena Pharmaceuticals Press Release, 2012).

### 3.2. Qnexa

Fixed-dose drug combinations to treat obesity have been pursued by Orexigen and Vivus on the basis that using already approved CNS compounds would help allay the safety concerns of the regulatory agencies. Furthermore, by employing drugs with complementary mechanisms it may be possible to achieve additive or even synergistic weight-loss with such combination therapies. Qnexa® (Vivus) consists of phentermine, which is a generic, non-selective, monoamine releasing agent (Prow et al., 2001; Tao et al., 2002; Rowley et al., 2000) that has been widely prescribed as a short-term appetite suppressant, combined with topiramate, which is a marketed anticonvulsant that was also clinically

<table>
<thead>
<tr>
<th>Table 2</th>
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<tr>
<td><strong>A comparison of the metabolic benefits of treatment with lorcaserin, Contrave®, and Qnexa® determined 1-year after treatment commencement.</strong></td>
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<tr>
<td><strong>Placebo-subtracted effect</strong></td>
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<td><strong>(10 mg bid)</strong></td>
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<tr>
<td><strong>Weight-loss (kg)</strong></td>
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<td><strong>Δ BMI</strong></td>
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<tr>
<td><strong>Categorical analysis of weight-loss</strong></td>
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<tr>
<td><strong>≥5%</strong></td>
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<tr>
<td><strong>≥10%</strong></td>
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<tr>
<td><strong>Lipid parameters</strong></td>
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<tr>
<td><strong>Total cholesterol (mg/dl)</strong></td>
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<td><strong>LDL-C (mg/dl)</strong></td>
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<td><strong>HDL-C (mg/dl)</strong></td>
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<tr>
<td><strong>Glycemic control</strong></td>
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<tr>
<td><strong>Fasting insulin (μIU/mL)²</strong></td>
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<tr>
<td><strong>Haemoglobin A1C (%)</strong></td>
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<tr>
<td><strong>Systolic (mmHg)</strong></td>
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<tr>
<td><strong>Blood pressure</strong></td>
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<tr>
<td><strong>Diastolic (mmHg)</strong></td>
</tr>
</tbody>
</table>

**ND** = Not determined; **DNA** = Data not available; **HoMA** = homeostasis model assessment; **HbA1c** = Haemoglobin A1c.

Sources: Lorcaserin new drug application [NDA] (2010); Arena Press Release (2010); Contrave NDA (2010); Qnexa NDA (2010).

* Result calculated from APD356—009 [BLOOM] data.
* Pooled result for all Phase 3 trials.
* Stated to be unchanged in Arena Press Release (2010).

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evaluated for the treatment of obesity (Astrup and Toubro, 2004; Bray et al., 2003; Rosenstock et al., 2007) until its development in this indication was halted because of unacceptable side-effects. The pharmacological mechanism underpinning topiramate’s weight-loss effect has not been fully elucidated, but may derive in part from potent inhibition of mitochondrial carbonic anhydrase V (Vullo et al., 2004). Jackson et al. (2007) demonstrated that either phentermine or topiramate produced substantial weight-loss in the cafeteria-fed dietary-induced obese (DIO) rat when given alone and when given in combination their effects were additive, but not synergistic. The weight-loss of the phentermine/topiramate combination in the DIO rat was greater than that observed previously with sibutramine, rimonabant or orlistat (Jackson et al., 2007). Three different dosage combinations of Qnexa have been clinically evaluated, i.e., phentermine (mg)/topiramate (mg): 3.75/23 (low dose), 7.5/46 (mid dose) and 15/92 (full dose). Consistent with the animal data, the weight-loss effects of combined phentermine and topiramate were shown to be approximately additive in a 6-month, Phase II trial (Vivus Press Release, 2010) and with 42% of patients achieving ≥10% placebo-subtracted weight-loss, the efficacy of Qnexa was considerably better than that reported for orlistat, sibutramine, or rimonabant (Van Gaal et al., 1998; Bray et al., 1999; Van Gaal et al., 2005; Despres et al., 2005; Pet-Sunyer et al., 2006). Two, large, 1-year Phase 3 pivotal trials have been performed with Qnexa. The first (OB-302) was in severely obese subjects (BMI ≥40 kg/m²) and the second (OB-303) was in overweight or obese subjects with co-morbid disorders, i.e., hypertension, dyslipidaemia or Type 2 diabetes together with abdominal adiposity. The placebo-subtracted weight-loss at 1-year observed after treatment with the full doses of Qnexa was 10.9 kg (9.4%) and 8.9 kg (8.6%) in OB-302 and OB-303, respectively (Table 2). After correction for placebo, the proportion of subjects on the full dose of Qnexa who achieved a ≥10% reduction in bodyweight from baseline was ~40% in both trials (Table 2). A summary of the benefits of Qnexa on cardiovascular risk factors is summarised in Table 2. The observed improvements in plasma lipid profiles, glycaemic control and blood pressure were consistent with the high degree of weight-loss and are substantially greater than those produced by lorcaserin because of Qnexa’s superior weight-loss effect (Table 2). Adverse events associated with Qnexa treatment were generally consistent with those reported for phentermine, i.e., dry mouth, constipation, insomnia, and palpitations, and for topiramate, i.e., dizziness, paresthesia, and disturbances in attention, together with headache, dysgeusia (distortion of sense of taste), alopecia and hypokalemia (Qnexa NDA, 2010). In addition, phentermine is a Controlled Drug (Schedule 3 and 4 in USA and UK, respectively). In spite of Qnexa’s impressive efficacy as an anti-obesity treatment, the FDA declined to approve the drug because of safety concerns.

Many antiepileptic drugs including topiramate are known to cause birth defects in humans and as the prescribing of anti-obesity drugs is predominantly to females in the 35–55 year age group, the safety concerns of FDA were well founded. However, the issue is complex because the doses of topiramate used in Qnexa are much lower than those required for the management of epilepsy, there were significant differences across the epidemiological data-bases that have estimated the teratological risks of antiepileptic drugs, and epilepsy itself is associated with an increased number of birth defects. Vivus is addressing these questions by conducting a retrospective review of the incidence of birth defects in woman taking topiramate during pregnancy. In the meantime, the company submitted a revised NDA in October 2011 for the use of Qnexa in the treatment of obesity in men and women without child-bearing potential (Vivus Press Release, 2011) with a view to extending the labelling to include all women if the results from its retrospective analysis are supportive. In terms of weight-loss and metabolic benefits, Qnexa is the leader of the current crop of pre-registration drug candidates and is almost certainly superior to orlistat, rimonabant and sibutramine.

3.3. Contrave

Contrave (Orexigen) is a fixed-dose combination of bupropion + naltrexone. Bupropion is a weak, selective dopamine reuptake inhibitor (Richelson and Pfennig, 1984) used to treat depression (Wellbutrin®) and as an aid to smoking cessation (Zyban®) and naltrexone is a non-selective opioid receptor antagonist used to treat opiate and alcohol dependence syndromes (Vivitrol®). Four pivotal trials have been conducted to evaluate Contrave in obesity. NB-301 to NB-303 were in subjects with uncomplicated obesity, or overweight/obesity combined with controlled hypertension and/or dyslipidaemia. NB-304 was a trial in overweight and obese subjects with Type 2 diabetes. At Week 56, the placebo-subtracted weight reductions observed with Contrave (naltrexone 32 mg + bupropion 360 mg) were 4.8 kg and 5.2 kg in NB-301 and NB-303 (Table 2). In NB-302 that included intensive dietary and behavioural support, the drug produced a 4.2 kg reduction in weight and in obese subjects with Type 2 diabetes, Contrave produced a 3.4 kg weight-loss. The proportion of subjects in NB-301 – NB-303 who achieved a ≥10% reduction from baseline bodyweight was 18–22% (Contrave NDA, 2010; Table 2).

In general, the improvements in various obesity-related, cardiovascular risk factors produced by Contrave were commensurate with the degree of reduction of bodyweight (Table 2). In obese diabetics, Contrave reduced plasma HbA1c by almost 0.5% (Contrave NDA, 2010). The major problem for Contrave was blood pressure did not decrease in-line with weight-loss and compared with equivalent weight-loss on placebo, Contrave produced small mean increases in both systolic blood pressure (SBP) and diastolic blood pressure (DBP) (Table 2). In addition to having a propensity to increase blood pressure, Contrave slightly increased the incidence of hypertension and palpitations. The most frequent side-effects of this drug were gastrointestinal that are likely to be linked to the opiate antagonist actions of naltrexone (Contrave NDA, 2010) http://www.fda.gov/downloads/advisorycommittees/committmeetingmaterials/drugs/endocrinologicalandmetabolicdrugsadvisorycommittee/ucm235671.pdf). Other adverse events included headache, dizziness, insomnia, and dry mouth (Contrave NDA, 2010) that probably derive from bupropion’s pharmacology as a catecholamine reuptake inhibitor. Although the FDA’s Advisory Committee voted to recommend approval of Contrave, the FDA declined the application in Feb, 2011 because of the safety risk to patients from increases in blood pressure. The agency has said that it wishes to see acceptable data for Contrave from a long-term cardiovascular outcome trial before it would grant approval of this anti-obesity medication. In the light of the recent withdrawal of sibutramine, which had similar effects on blood pressure, because of an increased incidence of non-fatal cardiovascular events, the decision by FDA looks reasonable and fair. Orexigen recently announced that it has reached a tentative agreement with the FDA over the design of the cardiovascular outcome trial and will conduct it with a view to resubmitting the NDA in 2013 or 2014 (Orexigen Therapeutics Press Release, 2011).

3.4. Summary

None of the recent NDA submissions has received approval by the FDA though each of these CNS anti-obesity drug candidates has a path to reach this goal. Broadening the discussion to include Europe, the EMA’s guideline for the efficacy of weight-loss drugs, i.e., ≥10% reductions from baseline maintained at 1-year that is also

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≥5% greater than achieved on placebo (EMA, 2007), is very different from the criterion employed by the FDA, i.e., ≥5% placebo-subtracted reduction in bodyweight (FDA, 2007). Although these criteria are the primary efficacy endpoints, both agencies will consider results from categorical analyses in their decision-making. On the basis of the information included in the NDAs, Qnexa is the only medication that would appear unequivocally to satisfy the EMA guidelines.

Even assuming that one or more of these new medications receives regulatory approval, in the real world, their contribution to combating the obesity epidemic will be determined by a number of factors that are briefly discussed here. It is now generally accepted that because anti-obesity drugs are treatments, not cures, they will need to be taken long-term, and as a consequence, maintenance of pharmacological effect is essential. In the case of Qnexa, there is good evidence to demonstrate that its weight-loss effect is maintained out to 2 years with no evidence of tachyphylaxis, i.e., the percentages of subjects (placebo-subtracted) who achieved ≥10% weight-loss on the high dose of Qnexa were 54.6% at Week-56 and 42% at Week-108 (Qnexa NDA, 2010). In contrast, the Year-2 results from the BLOOM trial revealed the worrying emergence of toler- ance to lorcaserin in the drug-responder group (Smith et al., 2010). Consistent with this conclusion, the difference between the percentage of patients who achieved ≥5% weight-loss on lorcaniser versus placebo decreased from 27.2% at Week-52 to 17.6% at Week-104. In the absence of indisputable evidence that pharmacotherapy in obesity reduces the long-term burden of illness or enhances life expectancy, the use of new anti-obesity drugs will be highly restricted by healthcare providers and/or patients will have to fund all or part of the costs of their treatments. In the latter situation, most patients equate efficacy with sustained, progressive weight-loss, and for many, the weight maintenance phase of treatment is considered to be a signal that the drug is no longer working. Since the majority of subjects are unlikely to achieve the high degree of weight-loss that they are seeking, it is questionable how willing they will be to pay for drugs that do not satisfy their expectations. These new medications could therefore follow the same marketing path as sibutramine and orlistat with a very high initial uptake of treatment that is followed by a quite rapid decline in prescription numbers.

4. New CNS approaches for treatment of obesity

In the CNS field, the major sources for potential anti-obesity compounds have been novel hypothalamic neuropeptide regulators and various monoaminergic targets. A list of current CNS targets with drug candidates in late-stage preclinical or early clinical development is shown in Table 3.

When assessing the potential of these new pharmacological targets and drug candidates, the translational validity of results from animal experiments to the human situation is critical to pharmaceutical R&D. In the case of obesity and related metabolic diseases, we are in the fortunate position that rodents are particularly well suited to the study of these disorders. Rodents are omnivorous and when fed a nutritionally well-balanced diet under laboratory conditions, they will maintain a reasonably healthy weight and body composition during adolescence and early adulthood. However, rodents find unhealthy, calorie-dense, sweet and/or high-fat foods irresistible and when given free access to such foods, they will overeat and gradually become grossly obese.
As described in a series of articles (Dickinson et al., 2001; Heal and Jagger, 2005; Heal et al., 2009, 2011), we have demonstrated that the cafeteria-fed, dietary-induced obese (DIO) female rat has exceptionally good predictive validity with 95% correlation between the magnitude of weight change produced by various anti-obesity and anti-diabetic drugs in clinical trials and their rank order for inducing weight-loss in this model. In addition to the DIO female rat, there are a number of other well validated rodent models of human obesity including the high-fat-fed, obese, growing, male rat and the DIO mouse and we will also discuss results obtained from these various paradigms.

4.1. Monoaminergic targets

4.1.1. Tesofensine

Tesofensine (NeuroSearch) is a potent, non-selective reuptake inhibitor of dopamine, noradrenaline and 5-HT, but there is relatively little information in the public domain describing its in vitro pharmacological profile. Tesofensine inhibits [3H]dopamine, [3H] noradrenaline and [3H]5-HT transport into synaptosomes with IC50 values of 6.5 nM, 1.7 nM and 11.0 nM, respectively (Lehr et al., 2008). A recently published article using a variant of the DIO rat model, tesofensine (0.5–3 mg/kg sc) dose-dependently reduced nocturnal food intake with an ED50 of 1.3 mg/kg (Axel et al., 2010). Pharmacological characterisation with selective monoaminergic receptor antagonists demonstrated roles for α2-adrenergic and dopamine D1 receptor-mediated neurotransmission in its hypophagic effect with no involvement of D2, D3, 5-HT2A/C or 5-HT1A receptor pathways. The selective catecholaminergic mode of action of tesofensine differentiates it from the mixed noradrenergic/serotonergic mechanism of sibutramine or the 5-HT2C receptor-mediated mechanism of lorcanerin and β-fenfluramine. When tesofensine (1 or 2 mg/kg po) was administered to DIO rats for 28 days, it reduced the bodyweight of these animals by 5.7% and 9.9%, respectively (Hansen et al., 2010). Sibutramine (7.5 mg/kg po), which was the reference comparator in this experiment, produced 7.6% weight-loss. If these results translate into clinical outcomes, tesofensine would have the potential to have equal or perhaps greater efficacy than sibutramine. Weight-loss induced by tesofensine in DIO rats was accompanied by improvements in metabolic status that included reductions in abdominal and subcutaneous fat mass, reductions in plasma lipids and increased insulin sensitivity (Hansen et al., 2010). Together this combination of an ability to decrease obesity and improve various cardiometabolic risk factors in a DIO rat model provided evidence to support its clinical development as a novel anti-obesity drug.

Tesofensine was initially taken into clinical development for the treatment of Parkinson’s or Alzheimer’s disease. Although clinically significant efficacy was not observed in either neurological condition, a meta-analysis of the results revealed that tesofensine (0.125–1.0 mg once daily) produced dose-dependent weight-loss in the combined patient group with ~32% of obese subjects on the highest dose of drug achieving ≥5% weight reduction after 14 weeks of treatment (Astrup et al., 2008a). The efficacy and tolerability of tesofensine was subsequently evaluated in a 24-week, randomised, double-blind, placebo-controlled Phase 2 trial in medically-uncomplicated obesity (BMI 30–40 kg/m²). Tesofensine was impressively effective in this trial producing mean placebo-subtracted decreases in bodyweight of 4.5 kg (2.5%), 9.1 kg (7.2%) and 10.6 kg (8.6%) with once daily doses of 0.25 mg, 0.5 mg and 1.0 mg, respectively (Astrup et al., 2008b). These reductions were accompanied by decreases in body fat and waist circumference and also modest improvements in plasma lipids. Dose-dependent increases in diastolic blood pressure and heart rate were noted on tesofensine treatment with placebo-subtracted mean increases of 1.5 mmHg and 7.4 bpm at the suggested clinical dose of 0.5 mg (Astrup et al., 2008b).

Psychiatric adverse events were also a potential cause for concern with 6.1% of subjects reporting depressed mood on the highest dose of tesofensine compared with 0% on placebo. Moreover, these adverse events occurred in a patient group that had been pre-selected to exclude those with known psychiatric disorders. Overall, tesofensine is impressively effective in terms of weight reduction. However, bearing in mind that rimonabant was withdrawn for the emergence of psychiatric adverse events and sibutramine was withdrawn for cardiovascular safety concerns, the challenge for this drug-candidate will be to convince regulatory agencies and prescribers that its safety profile is acceptable for approval and use as an anti-obesity drug.

4.1.2. 5-HT6 Receptor ligands

The 5-HT6 receptor-null mouse was discovered to be resistant to dietary-induced obesity (Caldirola, 2003) stimulating research into this receptor as a potential target for the development of new anti-obesity drugs. More recently, Frassetto et al. (2008) confirmed these findings. When fed a high-fat diet, 5-HT6 receptor knockout mice consumed approximately 8% less food than their wild-type counterparts, but gained about 35% less weight over an 11 week period. Body composition analysis of the mice showed that the reduced weight gain in the knockout mice was mostly due to decreased fat accumulation (Frassetto et al., 2008).

BVT-5182, synthesised by Biovittus, was the first 5-HT6 antagonist to have been extensively evaluated as a potential anti-obesity drug candidate. This compound was shown to decrease food intake when given acutely and chronically, to produce sustained weight-loss in dietary-induced obese (DIO) rats and mice and improve obesity-related cardiometabolic risk factors, eg visceral adiposity as well as blood leptin and insulin levels (Svartengren et al., 2003, 2004). Since those initial investigations, various other 5-HT6 ligands, e.g., BVT-71346, MEM68753 (Memory), SUVN-504 and SUVN-51005 (Suvlen) have also been demonstrated to produce improved cardiometabolic profiles in DIO rodents (Sastry et al., 2007; Svartengren et al., 2007; Shanmuganathan et al., 2008; Callahan et al., 2009).

In our laboratory, we have investigated the profiles of a number of 5-HT6 ligands in rodent models of obesity, the DIO female rat and the high-fat fed male rat models. They include the antagonists, PRX-07034 (Epix), MEM68626 (Memory), SB-742457 (CSK) and the partial agonist, E-6837 (Esteve). In these two models, substantial weight-loss was observed (Fig. 1) after repeated treatment with the 5-HT6 antagonists, PRX-07034 (Gannon et al., 2006a,b; Shacham et al., 2006). MEM68626 (Murray et al., 2008) and SB-742457 (Sargent, 2007), and also with the partial agonist, E-6837 (Fisas et al., 2006).

In the cafeteria-fed DIO rats, the 5-HT6 antagonist, PRX-07034 caused a sustained, progressive decrease in body weight (Fig. 1) when given chronically resulting in a 12.7% reduction after 6 weeks of administration (Gannon et al., 2006a,b; Shacham et al., 2006). The highest dose of PRX-07034 administered (10 mg/kg, ip, bid) produced a significant reduction of food intake in the animals for virtually all of the 6 week treatment period. A body composition analysis revealed that the reduction in bodyweight produced by PRX-07034 dosing was the result of a highly selective reduction in fat mass with minimal effects on either body water or protein content (Gannon et al., 2006b; Shacham et al., 2006). Consistent with a marked decrease in white adipocyte fat mass, plasma leptin concentrations in the PRX-07034-treated group of rats were decreased by more than 75% compared with the vehicle-treated controls. The reduced adiposity produced by administration of PRX-07034 improved glycemic control in obese rats with...
PRX-07034 – DIO females

SB-742457 – high fat fed, obese males

MEM68626 and sibutramine – DIO females

E-6837 and sibutramine – DIO females

Fig. 1. Effects of various 5-HT6 receptor ligands on body weight in the mature DIO females and high fat-fed, growing male rats

MEM 68626 10 mg/kg po bid
MEM 68626 30 mg/kg po bid
E-6837 and sibutramine – DIO females
E-6837 30 mg/kg po bid
Sibutramine 7.5 mg/kg po qd/vehicle po qd
MEM68626 and sibutramine – high fat fed, co-morbidities. Results are adjusted mean body weight vehicle-treated controls at the end of treatment. *p < 0.05, **p < 0.01, ***p < 0.001 versus controls. Data taken from: Gannon et al. (2006a,b), Murray et al. (2008), Sargent (2007), Fisas et al. (2006).

When assessed in the high-fat fed male rat model, PRX-07034 (100 mg/kg, po, bid) produced a reduction in body weight of 11.8% after 4 weeks. This was comparable to the weight-loss caused by sibutramine and better than rimonabant, which produced reductions of 10.4% and 6.5%, respectively (Gannon et al., 2006b; Shacham et al., 2006). PRX-07034 treatment also resulted in significant reductions of plasma leptin, glucose and insulin in these animals (Gannon et al., 2006b; Shacham et al., 2006).

One of the enigmas in the 5-HT6 field is that antagonists and agonists of this receptor subtype produce the same pharmacological effect on a number of CNS responses. Thus, it has been reported that cognitive function in the novel object recognition test is improved by both antagonists (Murray et al., 2008; Woolley et al., 2003; King et al., 2004; Vickers et al., 2004) and agonists (Kendall et al., 2010) and similarly, antidepressant-like effects in the mouse tail suspension test have been reported with the 5-HT6 receptor antagonist, SB 271046 (Svenningsson et al., 2007) in the mouse tail suspension test. SB-742457 and MEM68626 have both been evaluated in the high-fat-fed, obese, male rat where they produced dose-dependent reductions in body weight (Fig. 1). When MEM68626 was administered bi-daily to high fat-fed, obese male rats for 29 days, it produced a weight loss of 11.6% at the highest dose (Murray et al., 2008). SB-742457 produced a comparable weight loss in this model after only 8 days of oral dosing (Sargent, 2007).

The effects of MEM68626, SB-742457 and E-6837 (Murray et al., 2008; Sargent, 2007; Fisas et al., 2006) on weight loss in these rat models were compared with the anti-obesity drug, sibutramine (now withdrawn in Europe and the USA). The weight-loss effects of these three compounds were either comparable to, or in the case of E-6837, greater than sibutramine (15.7% weight-loss compared to 11% respectively) after 29 days of bi-daily dosing (Fig. 1).

Proof of principle for the obesity indication has been only obtained for the 5-HT6 antagonist, PRX-07034. In a randomised, double-blind, placebo-controlled Phase Ib trial in healthy obese adults, a placebo-subtracted weight-loss of 1.82 kg was observed after 28 days of treatment on 600 mg compound, twice-daily (Epix Press Release, 2007).

4.1.3. Compounds with monoamine reuptake inhibition and 5-HT1A agonist properties

5-HT1A agonists were first developed as centrally-acting hypertensive agents, but interest in the concept diminished when it was observed that tolerance rapidly developed to their beneficial effects. It was postulated that although 5-HT1A agonists were...
not suitable for development as novel antihypertensive drugs, they may be sufficiently effective to prevent the increases in blood pressure and heart rate produced by sibutramine (Heal and Cheetham, 2001). This concept was proven by demonstrating that sibutramine-induced increases in blood pressure and heart rate in conscious, telemetered rats were abolished by co-administration of the selective 5-HT₁A agonist, fllesinoxan. These findings formed the basis for a patent filing on this pharmacological combination (Heal and Cheetham, 2001). Prosidion also developed PSN-1 and PSN-2, which combined potent noradrenaline reuptake inhibition and 5-HT₁A agonism in the same molecule (Thomas et al., 2006). These compounds decreased food intake and produced weight-loss in both DIO female (Fig. 2) and high-fat-fed male obese rats (Thomas et al., 2006). The effects of PSN S1 (Fig. 2) and PSN S2 on bodyweight and food intake were similar in magnitude to those of sibutramine (Thomas et al., 2006). The weight-losses were mediated by a selective reduction in adiposity together with increased insulin sensitivity, but plasma lipid profiles were not altered (Thomas et al., 2006). PSN S1 was subsequently taken into clinical development, but the programme has now been discontinued.

4.2. Hypothalamic peptides

In the last twenty years, there has been an enormous expansion in the number of hypothalamic peptides that have been reported to play a role in the regulation of food intake and energy expenditure (Woods and Seeley, 2005; Hofmann and Tschöp, 2005). Although many of these hypothalamic peptides have been proposed as targets for the development of novel anti-obesity drugs, currently, there are very few candidates in clinical development and some very favoured approaches have failed to live up to expectations.

Neuropeptide Y (NPY) is a 36-amino acid peptide that is one of the most powerfully orexigenic hypothalamic peptides (Beck, 2006; Kamiji and Inui, 2007). For this reason, the development of novel, brain-penetrative, small molecule, compounds to block its actions was a scientifically logical approach to anti-obesity drug therapy that has been explored both preclinically and clinically (Kamiji and Inui, 2007). However, the pharmacology of NPY is complex and it exerts its actions in mammalian species via 6 distinct receptor subtypes (Y₁–Y₆) (Beck, 2006; Kamiji and Inui, 2007). Moreover, there has been some disagreement about which

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**Fig. 2.** Effect of the novel 5-HT₁A agonist and noradrenaline reuptake inhibitor, PSN S1, on body weight and food intake in the DIO female rat model of human obesity. Results are adjusted means ± SEM (n = 9–10). Figures in the upper graph represent percentage reductions of bodyweight compared with the vehicle-treated control group at Day 29. *p < 0.05 versus vehicle control group. Data taken from: Thomas et al. (2006).
NPY receptor is the most appropriate candidate for the development of novel antagonists with Y1 and Y5 subtypes being the most favoured (Beck, 2006). A number of pharmaceutical companies initiated programmes to synthesise novel Y5 antagonists and although several were shown to attenuate feeding behaviour and the development of diet-induced obesity in rodents, not all of the studies demonstrated their positive potential as anti-obesity drug candidates (Beck, 2006; Kamiji and Inui, 2007). In contrast to the positive findings obtained in some rodent studies, in a 52-week randomised, placebo-controlled, double-blind trial in obese adults, the Y5 receptor antagonist, MK-0557, produced weight loss that was statistically greater than placebo, but not clinically meaningful (Erondu et al., 2006). MK-0557 was found to be ineffective at preventing weight regain in obese subjects who had lost ≥6% of the baseline bodyweight after 6 weeks on a very low calorie diet (Erondu et al., 2007a) and it also failed to augment the weight-loss produced in obese subjects by sibutramine or orlistat (Erondu et al., 2007b). Based on this evidence, it appears that the sceptical view about the viability of the Y5 receptor as an anti-obesity drug target was correct. The Y1 receptor was thought to be a more relevant target for development and various potent Y1 receptor antagonists have been reported to inhibit food intake (Kamiji and Inui, 2007). However, many Y1-Y5 receptor agonists also display bioavailability and pharmacokinetics making them unsuitable for development. Although several new chemical series have been exploited in the search for better drug candidates (Kamiji and Inui, 2007), to the best of our knowledge, none of these compounds has entered clinical development.

Agonists of NPY Y2 and Y4 receptor subtypes have also been evaluated after it was discovered that the gut hormone, peptide YY (PYY), decreased food intake by stimulating hypothalamic Y2 receptors. Several groups have reported that infusion of PYY3–36 decreased food intake in lean and obese subjects when administered acutely (Kamiji and Inui, 2007). However, because this molecule is a polypeptide, finding a dosing formulation suitable for repeated administration posed a significant problem. PYY3–36 was found to have reasonable bioavailability when given in a nasal spray formulation, but in a 12-week, randomised, double-blind, placebo-controlled, clinical trial in healthy obese subjects, nasal administration of the lower dose produced only nominally greater weight-loss than placebo. The higher dose was not well tolerated mainly due to nausea and vomiting (Gantz et al., 2007). 7-TM Pharma, a biotech company specialising in the development of small molecule GPCR agonists and antagonists, has been actively working to discover novel ligands for various NPY receptors. TM30335 is a potent, highly selective, small molecule Y2 receptor agonist. In the DIO mouse model of human obesity, our laboratory has shown that repeated subcutaneous administration of TM30335 produced weight loss indistinguishable from that caused by PYY3–36 together with reductions in adiposity and plasma cholesterol concentrations (Elling et al., 2006, Fig. 3). Although, TM30335 may be much better suited to clinical development than a peptide, this compound is no longer listed on the company’s website. In the same scientific communication, Elling et al. (2006) reported that TM30339, which is a small molecule Y4 receptor agonist, produced profound weight loss in DIO mice that was greater than the effects of the Y2 agonists, PYY3–36 and TM30335 (Fig. 3). This compound also provided the metabolic benefits of reduced adiposity and plasma concentrations of cholesterol (Fig. 3). TM30339’s development status is listed as Phase 1/2 on 7-TM’s website. Finally, obin epitide (TM30358) is a dual Y2–Y4 receptor agonist that produces very substantial weight reduction in the DIO mouse model; in fact, its effect was considerably greater than that produced by the selective Y2 agonists, PYY3–36 and TM30335 (Elling et al., 2006, Fig. 3). In a clinical trial, obin epitide has been shown to be well tolerated and to suppress food intake for up to 9 h when administered to healthy obese individuals by subcutaneous injection (Elling et al., 2006). In December, 2011, obinepitide’s development status on 7-TM’s website was also listed as Phase 1/2.

Melanin concentrating hormone (MCH) is a 19-amino acid cyclic peptide and, in the CNS of mammals, this molecule is exclusively expressed in the lateral hypothalamus (Pissios, 2009). MCH has orexigenic effects and soon after the synthesis of the first MCH receptor antagonists, T-226296 (Takeda) and SNAP-7491 (Synaptic), these compounds were reported have powerful actions to reduce food intake and body weight in rodents (Pissios, 2009). There was also tentative evidence to suggest that MCH1 receptor antagonists modestly enhance energy expenditure by increasing resting metabolic rate (Itø et al., 2009). In DIO mice, AMR-MCH-1 (30 and 60 mg/kg po) was shown to produce profound and progressive weight-loss over 28 days (Sargent et al., 2008; Fig. 4). In contrast to sibutramine that was used as a positive control, not only was the reduction in body weight greater (AMR-MCH-1 = 11.1% and 13.9% at 30 and 60 mg/kg, respectively; versus sibutramine = 5.8%), but there was also continuous weight loss throughout the dosing of AMR-MCH-1 (Sargent et al., 2008; Fig. 4). Marked reductions in visceral adiposity were also observed after treatment with AMR-MCH-1 and sibutramine (Itó et al., 2009; Fig. 5). More recently, another potent MCH1 antagonist, AMR-MCH-14 (5 and 15 mg/kg po bid), has been reported to induce dose-related weight-loss in the DIO mouse that resulted in a 21.8% fall with the higher dose; an effect that was 3 times greater than that observed with sibutramine (Surman et al., 2009; Fig. 4). Fig. 5 shows that AMR-MCH-14 markedly decreased the plasma concentration of leptin indicating a substantial reduction in fat mass and this was accompanied by reductions in atherogenic plasma lipids (Surman et al., 2009; Fig. 5). A major setback to exploiting this drug target was an inability to synthesise potent, selective MCH1 antagonists that lack affinity for the hERG (human ether-a-go-go related gene) ion channel (Berglund et al., 2009). Albany Molecular appear to have overcome this problem and have recently reported on several chemical series that contain potent selective MCH1 receptor antagonists with reduced hERG affinity (Surman et al., 2010; Hadden et al., 2010). We have shown that examples of compounds from each of these series produced marked weight reductions when administered repeatedly to DIO mice (Surman et al., 2010; Hadden et al., 2010; Henderson et al., 2010).

The melanocortin 4 (MC4) receptor subtype is present not only on the hypothalamus, but it is also widely distributed across other regions of the mammalian brain. Signalling via MC4 receptors in the hypothalamus is tonically regulated by the actions of the endogenous agonists, αMSH, βMSH and γMSH, and antagonist, agouti-related protein (AgRP) (Adan et al., 2006). Intracerebral administration of the natural agonist, αMSH, or the synthetic agonist, melanotan-II (MTII), was found to decrease food intake and body weight in wild-type mice, but not in MC4 knockouts (Adan et al., 2006) suggesting that agonists of this receptor may have utility in the treatment of obesity. Designing and synthesising small molecule agonists for GPCRs where the endogenous ligand is a large peptide poses a much greater challenge than discovering peptide receptor antagonists. Nevertheless, several pharmaceutical companies, including Merck, have succeeded in this objective. MK-0493 is a potent selective MC4 receptor agonist with orally bioavailability (Krishna et al., 2009). In human volunteers, MK-0493 produced a significant reduction in calorie intake, but the effect was much smaller than that of the reference comparator anti-obesity drug, sibutramine (Krishna et al., 2009). In placebo-controlled clinical trials in overweight and obese subjects, a fixed dose of MK-0493 produced a small reduction...
from baseline body weight at 12 weeks, but the effect was not significantly different from placebo. In an 18-week trial employing a stepped titration dosing protocol for MK-0493, the same outcome was observed (Krishna et al., 2009). On this basis, the authors concluded that MC4 receptor agonism would not be a viable approach for developing novel drugs to treat human obesity.

In summary, research into hypothalamic peptides has exponentially increased our knowledge about the multiplicity of systems within the CNS that regulate energy intake and expenditure. Many of these potential drug targets have yet to be tested within a clinical setting. Although there have been some disappointing failures in the clinic, NPY Y2, Y4, and dual Y2–Y4 receptor antagonists, and MCH1 antagonists appear to show promise as potential new CNS approaches to obesity treatment.

### 4.3. Fixed-dose combinations

#### 4.3.1. Empatic (bupropion SR + zonisamide SR)

Empatic® (bupropion SR + zonisamide SR) is the second fixed-dose combination medication being developed by Orexigen. Empatic has completed its Phase 2 proof-of-concept evaluation. The pharmacology of the catecholamine reuptake inhibitor, bupropion, has been described in the section on Contrave. Zonisamide (Zonegran®) is an anti-convulsant drug with an unresolved pharmacological mechanism of action. Weight-loss is a known side-effect associated with the use of zonisamide in epilepsy and this property prompted a preliminary evaluation of its value as an obesity treatment. Gadde et al. (2003) conducted a small, double-blind, placebo-controlled trial of zonisamide in moderately obese, healthy subjects and reported a mean 5.0 kg

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**Fig. 3.** Effect of Y2 and Y4 receptor subtypes on the body weight, plasma cholesterol and fat content of male DIO mice. Data are adjusted means ± SEM that have been calculated from the residuals of the statistical model. First day of dosing was Day 1. Significantly different from appropriate vehicle-treated control group: *p < 0.05, **p < 0.01, ***p < 0.001 Dunnett’s test. Data taken from Elling et al. (2006).
(5.0%) placebo-subtracted reduction in body weight at the end of 16 weeks of treatment indicating its potential usefulness as an anti-obesity drug. Zonisamide, like topiramate, is a potent inhibitor of carbonic anhydrase isoenzymes and this pharmacological mechanism has been proposed to mediate its metabolic effects (De Simone et al., 2008). Orexigen employs a novel sustained release formulation of zonisamide that they have stated reduces its potential to cause adverse events. A 7-arm, 24-week, dose-ranging, proof-of-concept trial revealed that the high dose of Empatic (bupropion 360 mg + zonisamide 360 mg) produced a substantial, placebo-subtracted, weight-loss of 7.5% at the end of treatment (Orexigen Therapeutics Press Release, 2007). More recently, Orexigen reported results from a second Phase 2 trial evaluating high (bupropion 360 mg + zonisamide 360 mg) and medium (bupropion 360 mg + zonisamide 120 mg) doses of Empatic showing placebo-subtracted weight-losses of 6.1% and 4.7%, respectively, at 24 weeks (Orexigen Therapeutics Press Release, 2009). When these results are viewed as a categorical analysis, 20.7% and 28.3% of subjects achieved >10% reduction of their baseline weight on the medium and high doses of Empatic (Orexigen Therapeutics Press Release, 2009). Common adverse events reported for Empatic were headache, insomnia and nausea which are consistent with the known properties of the constituent drugs (Orexigen Therapeutics Press Release, 2009). In the light of the FDA’s negative opinion on the cardiovascular profile of Contrave and the fact that bupropion comprises one of the active moieties in both
combination products, a key piece of information that is not yet in the public domain is what effect Empatic had on blood pressure in these clinical trials. Overall, the clinical evidence indicates that Empatic and Contrave are approximately equivalent in terms of efficacy, but a more critical point is whether Empatic has less adverse influence on blood pressure than Contrave. Development of Empatic is currently on hold while Orexigen concentrates its resources on agreeing and conducting the cardiovascular outcome trial that is the key to the US approval of Contrave.

4.3.2. Pramlintide + metreleptin

Amylin Pharmaceuticals successfully developed pramlintide (Symlin®), which is a synthetic analogue of the pancreatic peptide, amylin, for the management of Type 2 diabetes. In obese human volunteers, injections of pramlintide three times daily prior to meals resulted in significant reductions in meal size with reduced cravings for food (Smith et al., 2007). After 43 days on this regime, pramlintide-treated subjects experienced a ~2.0 kg decrease in bodyweight (Smith et al., 2007). Because pramlintide delays gastric emptying, nausea is a common side-effect that could have contributed to reduced food intake; however, although the severity of nausea was higher with pramlintide treatment than placebo, this adverse event was not responsible for the reduction in calorie intake (Smith et al., 2007). In a 16-week, Phase 2 trial in obese subjects with or without Type 2 diabetes, pramlintide (240 μg tid) produced placebo-subtracted weight-losses of 2.4% (~2.4 kg) in diabetic subjects and 2.8% (~2.8 kg) in non-diabetics (Aronne et al., 2007). The authors also showed that the overall reduction in body weight was similar in subjects with and without persistent nausea confirming that weight-loss was not mediated by this side-effect (Aronne et al., 2007). In a 4-month, Phase 2B trial in non-diabetic, obese subjects that also included a single-blind 8 month extension period, twice daily dosing of pramlintide (240 μg) was found to be as efficacious as the three times daily regime (Smith et al., 2008). The conservative, ITT-LOCF analysis recorded a placebo-subtracted weight-loss of ~4.0 kg that realistically was
not sufficient to support clinical development as a monotherapy. Amylin subsequently explored its anti-diabetic drug, pramlintide, combined with metreleptin (recombinant human methyl leptin) for the treatment of obesity. The former neuro-hormone is a hindbrain satiety signal and the latter is a hypothalamic regulator of long-term energy homeostasis. Leptin is a regulatory hormone that is released into the bloodstream by adipocytes, which regulates food intake and energy expenditure by activating leptin receptors in the hypothalamus. Deficiencies in leptin signalling underpin the profound genetic obesity present in the Zucker fafja rat and ob/ob mouse. Initial enthusiasm about leptin’s potential as a wonder treatment for obesity was dashed by disappointing efficacy in clinical trials (Heymsfield et al., 1999); a finding that fitted with the observation that rather than having low levels of leptin, obese subjects had very high circulating levels of this hormone indicating that polygenic human obesity is associated with leptin resistance rather than leptin deficiency (Toornvliet et al., 1997; Bennett et al., 1997). Experiments performed in obese rodents revealed complex metabolic interactions between pramlintide and metreleptin with the former restoring impaired leptin signalling in the hypothalamus and the combination having a synergistic action to reduce body weight and adiposity (Trevisakis et al., 2008; Roth et al., 2008). Larcosarin et al. (2009) reported a 24-week, dose-finding study in obese subjects where the efficacy of the pramlintide (360 µg bid) + metreleptin (5.0 mg bid) was compared against the individual treatments. Because no placebo arm was included in the trial, the results were reported as reduction of weight compared with baseline. The ~12.0 kg reduction observed with the fixed-dose combination was greater than the ~8.0 kg recorded in the subjects receiving either pramlintide or metreleptin alone, but less than the sum of their effects. Amylin conducted a second Phase 2 trial using a placebo-controlled, multi-dose, multi-arm design, and showed that after 28 weeks, the pramlintide (360 µg bid) + metreleptin (5.0 mg bid) combination produced a placebo-subtracted 8.2 kg reduction in the weight of moderately obese subjects (Amylin Pharmaceuticals Press Release, 2009). This result was the less conservative completers’ analysis and the ITT-LOCF data were not provided in the press release. In all of these trials, the most commonly reported adverse events were nausea and injection site reactions. Although the results show that the pramlintide/metreleptin combination delivered efficacy that was equivalent to many other centrally-acting drugs and better than some, the requirement for twice-daily injections remained a significant barrier to patient acceptance. Following the report of an antibody-related safety issue, Amylin suspended its clinical trial and discontinued development of the pramlintide/metreleptin combination in 2011 (Amylin Pharmaceuticals Press Release, 2011).

5. Conclusions

The treatment of obesity with powerful centrally-acting drugs is an area where the question of whether the benefits justify the risks is debatable based on past experiences of poor safety with many of these agents. Furthermore, no clinical outcome study has yet been performed which demonstrates that long-term treatment with anti-obesity drugs has a positive effect to reduce rates of morbidity and mortality in obese subjects. The modest efficacy of current anti-obesity drugs causes prescribers and patients to question the value of drug treatment, and based on the available clinical data, this hurdle does not appear to have been overcome by eitherlorcaserin or Contrace. The uncertainty that still surrounds the US approvals of lorcaserin, Qnexa and Contrace is unsettling because it feeds the belief that the current safety barriers are so high and the appetite for new pharmacological treatments so low, it is impossible to get a new drug registered for the obesity indication. This assessment is incorrect and unfair to the regulatory agencies that have provided very balanced reviews of the latest drug candidates and appear very willing to work with the Sponsors to address their concerns. As demonstrated by the other reviews and original articles contained in this issue, a wealth of preclinical research has been undertaken that has provided a far greater understanding of the complex nature of the hypothalamic regulation of food intake, and in turn, it has generated a wide range of new molecular targets for the development of drug candidates to treat obesity. Although many of these approaches are still at a very early stage of development, several of these clinical candidates, e.g., 5-HT4 antagonists and partial agonists, MCH1 antagonists and various NPY agonists, have yielded results in preclinical models of obesity that predict they have the potential to deliver greater weight-loss than existing drugs. The discontinuation of several drug candidates in clinical development demonstrates the careful balance that needs to be drawn between efficacy versus tolerability and/or safety in order to achieve an acceptable benefit/risk profile in the indication of obesity. With the rates of obesity showing no signs of slowing, it has to be hoped that some of the drug candidates that are currently in development will form part of a new generation of anti-obesity drugs with increased efficacy and safety that is so urgently needed.

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D.J. Heal et al. / Neuropharmacology xxx (2012) 1–15

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