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REVIEW

The unrelenting fall of the pharmacological treatment of obesity

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Abstract Nowadays pharmacological therapy to limit obesity has reached a critical stage: not only have Authorities limited the use of antiobesity drugs due to their proven inefficacy and dangerous side effects, but bariatric surgery has delivered better results. At present, when the number of obese subjects is growing exponentially worldwide and more and more pathological mechanisms inducing fat accumulation have been discovered, no drugs are available to help patients and physicians to limit one the most dreadful causes of death. Following the failures of promising drugs as sibutramine and rimonabant, many companies stopped to invest in the field of obesity pharmacotherapy. At the same time, leading Authorities have started to require more solid evidence before providing authorization for these drugs to enter the market. This review aims at revising the failed promises of antiobesity drugs and describing the few potential future candidates in order to shed some light in the still uncertain field of antiobesity drugs. It also provides a critical contribution to the ongoing debate among scientists, clinicians, patients and Authorities on the possibility to treat obesity with pharmacological drugs.

Keywords Obesity · Drugs · Pharmacological therapy · Safety

Introduction

Obesity, as defined by body mass index (BMI) $\geq$30 kg/m^2, is widely considered as an emerging public health problem. As clearly showed in the surveillance of chronic disease risk factors (SURF) report 2, issued by WHO, there are currently over 300 million obese and over 750 million overweight people in the world. The relationship between obesity and co-morbidities such as type 2 diabetes, cardiovascular diseases, and cancer has becoming alarming; about 2.5 million deaths are attributed to obesity consequences [1]. This obesity epidemic has lately become particularly noticeable in medium- and low-income countries, mainly because of more palatable, lipid-rich, and low-cost food. However, as shown in recent published data, the increasing trend of BMI in the US population observed in the 2003–2008 period has reached its plateau [2]. This data could partly be explained by the efficacy of preventive strategies in the last years. Among the 19 Member States of the European Community, the global prevalence of overweight and obesity has risen up to 56 % for women and 69 % for men [3]. Globally, the World Health Organisation (WHO) has predicted that, by 2015, 2.3 billion adults will be overweight and 700 million will be obese. Data concerning school age children are even more dramatic with obesity/overweight prevalence estimated to increase up to 200 million [4]. Overall, these data show that obesity is an emerging problem for public health, with serious economic implications. It should be considered a chronic disease requiring long-term and effective treatment.

Traditionally, the possible therapeutic options to treat obesity are lifestyle interventions, pharmacological drugs and, last but not least, bariatric surgery.

Lifestyle intervention is the first recommended step to fight obesity, mainly because of its low rate of complications. As clearly showed in a recent exhaustive meta-analysis, changes in lifestyle are effective and safe in terms of weight gain [5]. In the 38 trials examined, patients treated with lifestyle intervention showed a significant

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weight loss, with an average of 4 % from the baseline weight. However, none of these studies include data on the maintenance of the weight lost in a long-term follow-up. Moreover, although lifestyle modifications have shown positive effects on diabetes and glucose tolerance, no study included in the meta-analysis has demonstrated that these changes play a role in mortality rates, cardiovascular diseases, and hospitalization. It should, however, be noted that a very recent, multicenter trial in Spain has showed that a Mediterranean diet supplemented with extra-virgin olive oil or nuts reduces the incidence of major cardiovascular events in people at high cardiovascular risk [6]. The lack of long-term data on cardiovascular outcomes is even more important considering the recent U.S. Food and Drug Administration (FDA) statements on the goals of obesity treatment (see below). Moreover, every experienced physician knows how difficult it is to change patients' lifestyle, especially in a long-term view.

Surgical treatment is the most effective treatment option available at the moment for obesity. It has been shown that bariatric surgery is more effective than lifestyle intervention in the treatment of morbid obesity [7]. Some of the most significant data on bariatric surgery come from a large long-term follow-up study named SOS [8]. This prospective, non-randomized, interventional trial involving 4,047 subjects shows that concerning weight loss, maintenance of weight lost, cardiovascular risk factors, incidence of diabetes, hypertension, and dyslipidemia those that had bariatric surgery compared favourably with the non-surgical group. Moreover, after several years of follow-up, surgically treated patients showed a lower incidence of myocardial infarction, stroke [9], cancer (only women) [10] and a lower overall mortality rate, in comparison to control patients [11]. The surgical treatment for obesity has also shown impressive results in terms of improvement in insulin resistance [12] and, more importantly, in terms of diabetes recovery, with remission rates ranging from 48 % in laparoscopic adjustable gastric banding up to 98 % in biliopancreatic diversion [13]. The mechanisms involved in the improvement and remission of diabetes are mainly due to the change in incretin levels (and probably other gut hormones, such as PYY_{3-36} and oxyntomodulin) observed after bariatric surgery [14]. These striking results have recently led to the revaluation of the strict BMI cut-offs for bariatric surgery for the prevention of diabetes and improvement of cardiovascular risk factors [15].

The increasing and long lasting clinical success of bariatric surgery in the last years, however, should not be taken as impacting negatively on the development of antiobesity drugs. Indeed, despite these encouraging results, bariatric surgery cannot be undertaken by all obese patients, because of the strict inclusion criteria [16, 17], the rate of surgical-related short- and long-term complications, and the costs of the surgical intervention, although this last issue has been challenged [8].

History of antiobesity drugs

The history of antiobesity drugs is characterized by an unusual high number of failures in achieving net final results in terms of body weight reduction and by an even more frequent presence of side effects that largely dominate on positive results. What follows is a concise review of the major failures in pharmacotherapy treating obesity.

Thyroxin and triiodothyronine

Pharmacological therapy for obesity has a long history, which started in 1893 when derivatives of thyroxin were used as antiobesity drugs [18]. Thyroxine and triiodothyronine used to treat obesity were withdrawn from the market in 1949 for their serious adverse effects, mainly thyrotoxicosis. Nowadays, several galenic or herbal products containing derivatives of thyroxine or jodine are still in use.

Dinitrophenol

The benzene-based compound 2,4-dinitrophenol (DNP) started to be used as antiobesity drug in the 1930s, after it was found that it caused weight loss as adverse effect to subacute exposure. This drug was largely used in US to treat obesity until 1938, when the FDA withdrew DNP from the market for its serious adverse effects, mainly hyperthermia [19]. This drug remains available as industrial compound; however, the side effects related to its illicit use in weight loss therapies are still reported in recent literature [20].

Amphetamine derivatives

Amphetamine derivatives, such as desoxyephedrine, methamphetamine, phendimetrazine, dietylpropion, benzphetamine, and mazindol, were the most prescribed antiobesity drugs in 1950s and 1960s. After 10 years, these centrally acting sympathomimetics suffered a market decline because of problems related to their tolerance, abuse, psychosis, and cardiovascular safety. In 2000, the European Medicine Agency (EMA) recommended their withdrawn from the market because of their unfavourable risk to benefit ratio [21]. However, the FDA still allows these drugs to be marketed in the US as short-term (few weeks) anorectic treatments in obese patients who do not respond to lifestyle modifications.

Phentermine, a noradrenaline and dopamine releasing agent, is an appetite-suppressant drug of the β-phenethylamine

family. This drug raised the same concerns about safety as the other amphetamine derivatives. As a consequence, it was withdrawn from the European market in 2001, whereas it is still available in the US, following the FDA approval of its short-term use (up to 3 months) in obese patients, in 1959. Phentermine has shown positive, though modest, effects on weight loss—an average weight loss of 3.6 kg compared to placebo [22]—in conjunction with lifestyle modifications, in short-term treatment regimens (from 2 to 24 weeks). Similar data were obtained in a more recent randomized, double-blind, placebo-controlled trial performed in 74 patients, treated for 12 weeks with phentermine diffuse–release–control [23]. Although the average weight loss in the treatment group was 9.3 kg respect to placebo, no data on efficacy, safety, and tolerability in the long-term period were available.

Diethylpropion is a phenylethylamine ring compound with minor sympathomimetic properties and fewer stimulant effects than amphetamine. It has been used as anti-obesity drug since its approval, in 1959. On top of changes in lifestyle, diethylpropion has shown modest effects on weight loss, with an average of 3 kg in the treatment group, as shown in the 13 randomized controlled trials (RCTs) conducted until 1983 [24]. A recent randomized, double-blind, placebo-controlled trial performed on 69 obese patients has shown the efficacy of diethylpropion in achieving a significant weight loss (10.6 % from the baseline) after 12 months of treatment [25]. However, no data on efficacy and safety in the long-term period (>12 months) are available.

As the other sympathomimetics, diethylpropion and phentermine have been withdrawn from the European market since 2000. Even if these are still marketed in the US with warnings and restrictions regarding the prescription in obese subjects, use of the sympathomimetic drugs is still monitored by the US Drug Enforcement Agency, because of concerns of their potential abuse.

Serotonin releasers/reuptake inhibitors

The first serotonin (5-HT) releasers and reuptake inhibitors were aminorex and fenfluramine. These were introduced in the European market in the early 1960s. Fenfluramine was introduced in the US market about 10 years later. Aminorex was short-lived; it was in fact withdrawn a few years after its release due to reports of primary pulmonary hypertension as serious adverse effect [18].

Fenfluramine and dexfenfluramine (the *d*-isomer of fenfluramine) exert an effect on obesity by suppressing appetite and reducing food intake. Despite their effects on weight loss, these antiobesity drugs were withdrawn from the market in 1997 after reports of pulmonary hypertension and cardiac valvulopathy [26, 27].

Fenfluramine and dexfenfluramine had also been used in combination with phentermine (fen-phen). This combination therapy led to more weight loss than placebo in a 28-week RCT (15.5 vs 4.9 %) [28]. However, the use of fen-phen has been associated to heart valve damage and pulmonary hypertension, as demonstrated in a report on 24 obese women [29]. As mentioned above, these drugs are no longer available in the US and European markets since 1997.

Sibutramine (Reductil®, Meridia®) is a norepinephrine and serotonin reuptake inhibitor approved in 1997 for weight control in patients who are unable to lose weight by diet or exercise alone. Sibutramine has shown satisfactory effects, with an average of 4.3 % of weight loss from the baseline, respect to placebo. Its effects on maintenance of weight have also been promising, as shown in a recent meta-analysis demonstrating that up to 30 % of patients treated with sibutramine were able to maintain their weight lost in a long-term follow-up (24–52 weeks) [30]. However, the main side effects related to the use of sibutramine were increased systolic and diastolic blood pressure, and increased pulse rate. For this reason, sibutramine was reviewed by the EMA in 2002 and was temporarily withdrawn from the Italian market after 47 adverse event reports (tachycardia, hypertension, and two deaths from cardiovascular diseases) [31]. Following these reports of adverse cardiovascular effects, the Committee for Proprietary Medicinal Products (CPMP) of the EMA reviewed the safety and the efficacy of sibutramine, concluding that the benefits of this drug outweighed the risks. However, the CPMP requested Abbott Laboratories to undertake the sibutramine cardiovascular outcome study (SCOUT) [32]. The SCOUT trial was a 5 year, randomized, double-blind, placebo-controlled multicenter trial involving 10,744 subjects with obesity, type 2 diabetes and history of cardiovascular disease. The main outcome was the evaluation of the time from randomization to the first cardiovascular event. The results of this trial were not encouraging, showing an overall incidence of serious, non-fatal cardiovascular events of 11.4 % in the sibutramine group respect to placebo [33]. After the publication of the preliminary results of the SCOUT trial, in January 2010 the EMA withdrew sibutramine from the European market [34] while the FDA allowed its use until the publication of the final results of the SCOUT trial, but restricted their prescription to patients without cardiovascular diseases. Despite the final results of the SCOUT trial have not shown an increased cardiovascular mortality, sibutramine was withdrawn from the US market by FDA in October 2010 [35].

Cannabinoid type 1 receptor antagonists

The discovery of the endocannabinoid system and its effects on appetite regulation, energy balance and reward

mechanisms have led to a new class of antiobesity drugs. Endocannabinoids are arachidonic acid derivatives that act as endogenous ligands for two main receptors, type 1 (CB1r) and type 2 (CB2r), widely expressed in the brain and in periphery [36]. The finding in the late 1990s that the CB1r blockade could lead to anorectic effects and increase energy expenditure, has lead to the development of rimonabant, a CB1r antagonist/inverse agonist [37].

Rimonabant (Acomplia®, Zimulti®) as antiobesity drug has been widely studied in several clinical trials for its efficacy in lowering body weight, improving glucose and lipid profile, and reducing cardiovascular risk factors.

The Rimonabant in Obesity (RIO) trial was a phase 3 trial evaluating the efficacy and safety of rimonabant. The results of this worldwide trial have been obtained through two 2-year studies (RIO-Europe and RIO-North America) and two 1-year studies (RIO-diabetes and RIO-Lipids).

The RIO-Europe and the RIO-North America were multicenter, randomized, placebo-controlled, double-blind trials involving more than 4,500 obese or overweight patients with hypertension or dyslipidemia. These trials have shown similar results in terms of efficacy in achieving significant weight loss and reduction in waist circumference, with patients taking rimonabant 20 mg respect to placebo [38, 39]. The positive effects on maintenance of weight lost and improvement of cardiovascular risk factors, as defined by metabolic syndrome, have been demonstrated after 2 year treatment with rimonabant 20 mg [39, 40]. The results in patients treated with rimonabant 5 mg were less striking.

The RIO-diabetes was a randomized, double-blind, placebo-controlled trial evaluating the treatment with rimonabant 20 mg in about 1,400 obese patients with type 2 diabetes inadequately controlled with metformin or sulphonylurea. As shown in previous trials, after 1 year of treatment, weight loss was greater in patients receiving rimonabant than in those receiving placebo. The treated patients also showed a mean reduction in glycated haemoglobin (HbA1C) of 0.7 % respect to placebo [41]. Similar results were also shown in a subsequent multicenter, randomized, double-blind, placebo-controlled trial involving 281 obese drug-naïve diabetic patients treated with rimonabant 20 mg [42].

The efficacy of rimonabant in improving lipid profile and cardiovascular risk factors has been confirmed in the RIO-Lipids study, a 1 year, randomized, double-blind, placebo-controlled trial. Besides weight loss and improvement in cholesterol and triglycerides levels, treatment with rimonabant has been shown to decrease plasma leptin and to increase plasma adiponectin [43].

Despite promising results in achieving significant weight loss and improvement of cardiovascular risk factors, as shown by RIO trials, the safety of rimonabant has been questioned. Patients treated with rimonabant have in fact experienced high rate of psychiatric adverse events, such as depressive mood disorders, anxiety, and suicidal ideation [44].

The safety concern of rimonabant with regard to psychiatric adverse events and suicidal ideation, has been widely questioned before the decision of the FDA to withdraw the drug from the US market. The decision of the FDA was replicated after 2 years by the EMA that sanctioned the withdrawn of rimonabant from the European market, in January 2009 [45].

The decision of the EMA caused the interruption of the first randomised, placebo-controlled trial, evaluating the effect of rimonabant in decreasing the incidence of cardiovascular events. In the CRESCENDO trial were enrolled 18,695 obese patients with coronary, cerebrovascular or peripheral artery disease; this study was prematurely interrupted in 2009, with no conclusive results [46].

Besides safety concerns about adverse effects, the efficacy of rimonabant has also been recently challenged by the results of a Phase 4 trial. The CARDIO-REDUSE study is a 1 year, double-blind, randomized, placebo-controlled trial evaluating cardiovascular risk factors in 372 obese patients treated with rimonabant. This study has shown significant weight loss and reduction in waist circumference in treated patients, without any other improvements in cardiovascular risk factors [47].

The psychiatric adverse events related to rimonabant treatment have been mainly attributed to the antagonism of the CB1r in the central nervous system (CNS). The recent research direction is therefore oriented towards the development of new compounds that act selectively in peripheral CBrs (see below).

Lipase inhibitor

Orlistat (Alli®, Xenical®) is a reversible pancreatic and gastric lipase inhibitor approved by FDA in 1998 for long-term treatment of obesity. The inhibition of pancreatic lipase leads to a reduction in fat absorption from the gut of about 30 % [48]. Orlistat has been shown to induce modest weight loss (mean values of about 3 kg after 12 months in the treatment group, respect to placebo) [22]. Notwithstanding this, treated patients have shown reduction in waist circumference, blood pressure, glucose levels, and lipid profile [49]. Orlistat has also been shown to reduce the incidence of type 2 diabetes from 9.0 to 6.2 % in the XENDOS trial [50]. Although orlistat is the only drug approved for long-term treatment of obesity in US and Europe, its use in the clinical practice is limited by gastrointestinal side effects, mainly steatorrhea. Recently, however, even the safety of orlistat has come under scrutiny, following reports of serious events in obese patients.

In 2010, the FDA revised the label for orlistat to include safety information about severe liver injury [51]. Moreover, orlistat has been associated with kidney and pancreas injuries [52].

Combination therapies

The combination of phentermine and topiramate controlled release (Qnexa®, Qsiva®, Qsymia®) has been widely studied in obese patients. Phentermine has been already described above. Topiramate is a drug used for treatment of epilepsy and migraine prophylaxis. The combination of these two drugs was attempted to avoid the effects of the multiple compensatory biological mechanisms occurring in the CNS. The positive effects of phentermine + topiramate controlled release on weight loss and obesity co-morbidities have been shown in a randomised, double-blind, controlled study known as CONQUER, involving 4,152 patients. This trial showed a significant weight loss in the two treated groups (with increasing doses of the drug) respect to placebo, with a mean weight loss of 8.1 and 10.2 kg, respectively; moreover, the prevalence of patients that achieved a weight loss of at least 5 % were 62 and 70 %, respectively [53]. The CONQUER study also showed improvement in lipid profile and reduction in systolic blood pressure in dyslipidemic and hypertensive patients [54]. Despite the encouraging effects of phentermine + topiramate controlled release on weight and cardiovascular risk factors, adverse effects reported on heart rate, adverse psychiatric events, as well as some concerns about foetal toxicity have led to the withdrawn of the drug from the European market by the EMA, in October 2012 [55]. For the same reasons, in November 2012 the FDA revised the label for phentermine + topiramate controlled release to include safety warnings on these topics [56].

FDA and EMA rules for approval of antiobesity drugs

The problematic history of the antiobesity drugs and the problems with their related side effects has led to severe restrictions on the approval of new drugs, by the FDA and EMA regulatory committees. Particularly, more restrictive rules started to be enforced in 2007, when it was established that approval of drugs for obesity treatment should be evaluated considering two main issues: efficacy in weight gain achievement and tolerability. According to the 2007 FDA draft guidance for industry entitled "Developing Products for Weight Management", the efficacy for an antiobesity drug is demonstrated if the following conditions are satisfied: (i) the difference in weight change from the baseline between the treatment group and placebo is ≥5 %, and (ii) the number of patients in the treatment group that obtain this weight gain is at least 35 % and approximately double the number of subjects in the placebo group [57].

Similarly, the EMA draft guidelines stated that the main objective for promoting weight loss in obese patients is to reduce the risk factors associated with this condition. Therefore, an antiobesity drug is considered effective if it produces: (i) a weight loss of at least 10 % of baseline weight; (ii) a magnitude of weight loss significantly different from the placebo group treated with lifestyle intervention. Improvement of cardiovascular risk factors and maintenance of weight lost should be considered appropriate secondary outcomes [58].

Despite the FDA and EMA guidelines, the previous outcomes were not considered reliable enough to approve the commercialization of antiobesity drugs, especially after the statement regarding the antidiabetic drugs issued by the Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC) for the FDA, in June 2008. The EMDAC considered a two-step process for evaluating the cardiovascular safety of these drugs, consisting of a randomized cardiovascular event-driven trial before approval, and a longer and larger trial after approval. Moreover, in order to reach an accurate evaluation with sufficient number of events occurring in a short space of time, it was pointed out that the preliminary trials had to be performed in the highest risk population [59]. Following this model, in March 2012, the FDA Advisory Committee established that the evaluation of antiobesity drugs should be made after their effectiveness in reducing cardiovascular risk had been assessed [60]. However, despite all these warnings and limitations issued by the European and US regulatory agencies for market approval, the research on new antiobesity drugs still continues.

Ongoing drugs (monotherapy)

Lorcaserin (Lorqess®, Belviq®)

Lorcaserin is a selective serotonin 2c (5-HT_{2c}) receptor agonist, which selectively activates the central 5-HT_{2c} receptors and decreases food intake through the proopiomelanocortin system of neurons [61, 62]. In June 2012, this drug has been approved by the FDA for use in patients with BMI ≥ 30 kg/m^2 or with BMI ≥ 27 kg/m^2 and with at least one co-morbidity (hypertension, type 2 diabetes or dyslipidemia) [63]. The main results concerning the effects of lorcaserin on body weight came from 3 RCTs performed between 2006 and 2009. The first study was the BLOOM trial, a 2 year, randomized, placebo-controlled, double-blind trial, performed on 3,182 obese or overweight/obese patients with at least 1 co-morbidity (hypertension,

dyslipidemia, cardiovascular disease, impaired glucose tolerance or sleep apnea). This study showed that almost half of patients receiving lorcaserin associated with lifestyle intervention lost ≥5 % of the initial weight within the first year of treatment. The average weight loss was 8.1 kg. At the end of the trial, the proportion of patients who maintained their weight lost was higher than placebo [64]. A further trial, BLOSSOM, was performed on 4,008 obese or overweight patients with related co-morbidities. Similarly to the BLOOM study, after 1 year of treatment, the proportion of patients achieving a weight loss ≥5 % was 47.2 and 40.2 % in the group of subjects receiving lorcaserin 10 mg BID and 10 mg once daily, respectively [65]. The missing data in diabetic patients, patients in which weight loss is considered more difficult because they are insulin-resistant, were soon supplied by the BLOOM-DM study. This consisted of a 1 year, randomized, double-blind, placebo-controlled trial performed on type-2 diabetic patients treated with metformin, sulfonylureas, or both. In the group of patients treated with lorcaserin 10 mg BID, the patients achieving ≥5 % of weight loss were 37.5 %, whereas those achieving ≥10 % were 16.3 % compared to placebo [66]. Although the improvement of HbA1C was not a primary goal in the BLOOM-DM study, almost half of the patients receiving lorcaserin showed an improvement of glycated haemoglobin (<7 %).

As with other non-selective serotonin receptor agonists used previously, because of its mechanism of action, the use of lorcaserin has raised some concerns about safety, with regard to the potential incidence of cardiac valvulopathy. However, none of the mentioned studies have shown an increased incidence of valulopathy in patients with or without type 2 diabetes treated with lorcaserin.

Therefore, compared to placebo, lorcaserin has shown to induce a significant, but still modest, weight loss after 2 years of treatment. Moreover, such a weight loss is achieved with a low rate incidence of cardiovascular, psychiatric, and gastrointestinal side effects [67].

Although lorcaserin is already available in the US market, its approval in Europe is still under evaluation of the Risk Management Plans (RMP) and for its market authorization by the Commission of Medical Products for Human Use (CMPHU) of the EMA [68].

Glucagon-like peptide-1 analogues

Glucagon-like peptide-1 (GLP-1) analogues are a class of drugs with similar structure to the human GLP-1. In recent years, they have been widely used for the treatment of type 2 diabetes, with convincing results in terms of improved metabolic control [69]. This class of drugs exerts its effects mainly in the gastrointestinal tract and in the brain. Similarly to other GLP-1 analogues used in clinical practice, liraglutide (Victoza®) has shown positive effects in HbA1C levels, β-cell vitality, and systolic blood pressure. This improvement has been associated with a dose-dependent weight loss, as confirmed by Phase 3 trials performed for this specific scope. The most striking results came from a 2-year extension of a 20 week, randomized, double-blind, placebo-controlled trial performed on obese non-diabetic patients. In this extension trial, involving about 600 subjects, patients treated with liraglutide have shown higher weight loss rates respect to placebo and orlistat, respectively, in a dose-dependent manner (up to 3.0 mg of liraglutide). The weight lost has been maintained until the end of the 2-year period, with a mean weight loss of 7.8 kg in patients treated with the higher dose of liraglutide, compared to subjects treated with orlistat [70]. The reduction in body weight was concomitant with the reduction in waist circumference and the improvement of indirect markers of cardiovascular risk, as in the previous 20-week Phase 3 trial [71].

Moreover, liraglutide has shown lower rates of discontinuation over the 2-year period (34–43 %) respect to many other antiobesity drugs tested in the past. The main side effects were gastrointestinal, mainly nausea and vomiting. However, the effects of liraglutide on weight loss have been of higher magnitude than those obtained with another analogue such as exenatide (Byetta®, Bydureon®), as shown in a recent 26-week, multicentre, open-label, randomized, parallel-group trial performed on 912 diabetic patients (DURATION-6 trial) [72].

Liraglutide and the other GLP-1 analogues have not yet been approved for obesity treatment.

Albiglutide, a GLP-1 receptor agonist, and taspoglutide, a GLP-1 analogue, have shown interesting results in diabetic patients in terms of weight loss [73]. However, Phase 3 trials in obese patients are still needed in order to assess the efficacy and safety of these compounds.

Zonisamide

Zonisamide is an antiepileptic drug, which has shown modest effects in achieving weight loss. The exact mechanism of action of this compound has not yet been completely established. The first report of its antiobesity properties was assessed in a 16-week trial completed by an extension phase of further 16 weeks [74]. The study was performed in obese patients who, after taking 400 mg of zonisamide, showed a mean reduction of body weight of 5.9 kg. A second study on zonisamide was performed to compare the efficacy of the 400 mg dosage, the 200 mg one, to placebo. Patients taking the lower dose of zonisamide were not able to lose more weight than placebo. Despite positive effects on body weight and waist circumference, no difference was found in other

cardiovascular risk factors after 1 year treatment with zonisamide [74]. Considering this issue, the real efficacy of this drug as antiobesity treatment has yet to be determined, especially considering the FDA and EMA guidelines regarding the marketing of new antiobesity compounds.

Tesofensine

Tesofensine is a monoamine reuptake inhibitor of dopamine, norepinephrine, and serotonin, structurally similar to the dopamine reuptake inhibitor cocaine [75]. This drug was initially developed as anti-parkinsonian compound, but did not have the expected results. It has instead shown positive effects on body weight loss. Tesofensine as antiobesity drug has been studied in Phase 2 trials and, as far as we know, no Phase 3 trials are ongoing at the time of this review. The effects of tesofensine in inducing weight loss are probably due to a reduction in appetite, without effects on energy metabolism, as shown in a recent Phase 2 trial [76]. The weight loss obtained with tesofensine in humans is promising, as shown in a randomized, double-blind, placebo-controlled, parallel-group study performed on 203 non-complicated and non-diabetic obese patients. In this study, increasing doses of tesofensine, up to 1.0 mg, induced a maximum mean weight loss of 10.4 %, compared to placebo after 6 months of treatment [77]. Waist circumference, insulin levels, and lipid profile were also improved. However, in patients treated with the higher dose of this drug, an increase in blood pressure and heart rate has been noted. These data were not surprising, considering the mode of action of this compound, which is very similar to that of sibutramine. The cardiovascular safety of tesofensine has also been questioned, leading to a need for Phase 2 and Phase 3 trials designed to investigate further this specific issue [78]. Up to now, studies on cardiovascular safety of tesofensine have not yet been proposed.

Ongoing drugs (politherapies)

Even after a successful significant achievement of weight gain, the effects of pharmacological therapy for obesity are often counterbalanced by the activation of compensatory biological signals. This is mainly due to complex net of mechanisms occurring in the CNS that regulate appetite and energy homeostasis [79]. Considering this, the politherapy for obesity seems to be more appropriate than monotherapy, because it can simultaneously (in)activate specific systems and their counter-regulatory mechanisms. As it also happens for hypertension and diabetes, the politherapy for chronic diseases could be extremely successful and, hence, should be considered an important research issue in obesity treatment, especially in a long-term view. Moreover, the combination of drugs targeting different systems allows a reduction of the dose of each compound, probably limiting the related adverse events, which is undoubtedly one of the main concerns with the approval of new antiobesity drugs.

Naltrexone sustained release (SR) + bupropion SR (Contrave®)

Naltrexone is a pure opioid antagonist whereas bupropion is a dopamine reuptake inhibitor, generally used as antidepressant. The exact mechanism by which this combination of drugs leads to weight loss has not yet been discovered. It has been hypothesized that both drugs interact with the hypothalamic melanocortin system and the mesolimbic reward system [80].

The efficacy and safety of naltrexone SR + bupropion SR has been evaluated in four Phase 3 trials in the Contrave Obesity Research (COR) setting.

The COR-I was a multicentre, randomized, double-blind, placebo-controlled trial evaluating the effect of naltrexone SR + bupropion SR in 1,742 non-complicated obese or overweight patients with hypertension and/or dyslipidemia. The study showed a weight loss of about 8 % from the baseline in treated patients, during the duration of the trial—56 weeks [81]. More encouraging results in terms of weight loss and percentage of patients achieving weight loss of at least the 5 % of body weight were shown in a similar Phase 3 trial [82]. The improvement in cardiometabolic risk factors related to obesity has been confirmed in the randomized, parallel-arm, placebo-controlled, COR-II trial, recently published [83]. The fourth Phase 3 trial, the COR-Diabetes trial, has not been published yet. This study was performed to assess the efficacy and safety of naltrexone SR + bupropion SR in obese patients with uncontrolled diabetes treated with oral antidiabetics [84]. Preliminary results confirmed the known effects of these drugs on weight loss (primary endpoint) and showed promising results in reducing HbA1C during the study period (−0.6 % from baseline for all treated patients respect to placebo and −1.1 % from baseline for treated patients with starting HbA1C >8 %) [85]. The beneficial effects of naltrexone and bupropion on weight loss, cardiovascular risk factors, and diabetes shown in these four trials were associated to modest side effects, such as nausea.

However, none of the published trials has been performed on complicated obese patients. According to the rules imposed by FDA, and because of the lack of data in complicated patients, an additional study on efficacy and safety of naltrexone SR + bupropion SR should be performed, with evaluation of major cardiovascular outcomes in obese patients as primary endpoint [86]. For this

purpose, a Phase 3, multicenter, randomized, double-blind, placebo-controlled trial (the Light Study) was started in July 2012 and is still ongoing. The Light Study is designed to assess the cardiovascular health outcomes of naltrexone SR + bupropion SR in overweight or obese patients with cardiovascular risk factors, such as heart disease or type 2 diabetes with certain heart risk factors [87]. The Light Study is estimated to finish in 2017.

Zonisamide + bupropion (Empatic®)

The combination of zonisamide + bupropion has been studied in a Phase 2, randomized, open-label, parallel-group trial evaluating the efficacy of this politherapy compared to zonisamide alone. The combination treatment was more effective in achieving weight loss than monotherapy [88]. Similar results were found in a 24-week randomized, controlled trial evaluating the efficacy in terms of weight loss of zonisamide + bupropion compared to zonisamide and bupropion alone, and to placebo, respectively [89]. Following promising results, the Orexigen® is planning to ask the FDA for a Phase 3 trial evaluating zonisamide + bupropion as antiobesity drug [90].

New therapies: the future of antiobesity drugs

The discovery of weight loss properties in GLP-1 has lead to a new approach to fight obesity. Considering the powerful effects of these drugs on achievement and maintenance of weight loss, the combination of GLP-1 analogues with other compounds targeting different receptors seems to be an intriguing strategy. Recently, a glucagon and GLP-1 co-agonist has been developed with promising results [91]. As other gastrointestinal peptides, glucagon has shown a role in the regulation of eating control and energy expenditure [92]. A glucagon agonist has been then combined to the GLP-1 to achieve higher potency in obtaining weight loss and to reduce the diabetogenic effects given by the glucagon agonist alone. This new compound has shown 25 % reduction in body weight in the short term (1 week) in diet-induced obese (DIO) mice. The weight reduction was mainly due to a decrease in average daily food intake. In long-term treated mice (1 month) the maintenance of the weight lost was mainly due to an increase in energy expenditure with a consequent reduction in body fat mass. Moreover, treated DIO mice have shown reduced blood glucose levels and improved insulin sensitivity, as demonstrated in an intraperitoneal glucose challenge [91]. These results have opened an intriguing perspective in the antiobesity drug research, leading to the possibility to develop a single molecule with multiple gastrointestinal peptides. Very recently, the first trial with a new treatment combining GLP-1 and glucagon has been proposed in humans. In a small proof of concept trial, 16 human volunteers were allocated to a sequence of four treatment infusions for 120 min, separated by at least 3 days each: (i) glucagon, (ii) GLP-1, (iii) glucagon + GLP-1 in combination, and (iv) saline infusion as control. Volunteers treated with the glucagon + GLP-1 combination consumed significantly less food. A non-significant trend towards increase in energy expenditure was also noticed in the glucagon + GLP-1 and in the glucagon alone groups [93].

Following the politherapy strategy, another GLP-1 related compound has been recently developed to enhance the weight loss properties of this gastrointestinal peptide. Differently from the combined therapy described above, this new drug has combined the anorectic effect of the GLP-1 to the metabolic properties of oestrogens, which has been shown to modulate energy expenditure and feeding behaviour [94]. The combination of oestrogens with GLP-1 as vehicle has led to the development of a therapy targeted to specific tissues (the ones with GLP-1 receptors), in order to selectively enhance the metabolic effects of the oestrogens avoiding their gynaecological and tumour-promoting actions. The stable GLP-1-oestrogen combination administered to DIO mice has shown 24 % reduction in body weight, mainly due to a decrease in food intake and in body fat mass. Positive effects were also shown in the lipids and glycemic profile. However, the stable GLP-1-oestrogen conjugate did not show any increase in energy expenditure. None of the treated DIO mice showed gynaecological side effects or tumours [95]. The discovery of this compound has introduced the concept of a targeted therapy for obesity, which could become a realistic approach in clinical practice.

In the wide panorama of antiobesity drugs, the role of compounds targeting the endocannabinoid system is still relevant, despite the withdrawal of rimonabant from the US and European markets. The CB1r, the main target of rimonabant, has been demonstrated in the CNS as well as in peripheral tissues [36], leading to the concept that regulation of body weight by the endocannabinoid system can occur with food intake-independent mechanisms. The pivotal role of the central CB1r has been clearly demonstrated in studies performed on conditional mutant mice, with selective CB1 deletion in the CNS [96]. In this study, the conditional KO mice has shown DIO resistance, mainly due to increased thermogenesis and hyperactivation of the sympathetic nervous system (SNS), despite the overall food intake was not different from the wild type. The increase in thermogenesis was generated by the enhanced activity of the brown adipose tissue (BAT), which is modulated by the SNS, as demonstrated by the loss of BAT activity after sympathectomy [96]. The discovery of the endocannabinoid system cross-talk between CNS and periphery has lead to the development of peripheral CB1r

antagonists as new targets for obesity treatment, avoiding the known side effects due to the central CB1r blockade.

Peripheral CB1r antagonists have shown promising results. AM6545 (Makriyannis Lab, Northeastern University), a potent and selective CB1r antagonist with limited brain penetrance, has demonstrated to improve glycemic control and dyslipidemia, and to reverse hepatic steatosis, without affecting body weight [97]. AM6545 has been also shown to improve leptin sensitivity. This weight independent change has strengthened the diversity of actions of the endocannabinoid system in the CNS and in periphery. TM38837 (7TM Pharma) is a second-generation CB1r peripheral antagonist recently studied in a double-blind, placebo-controlled, cross-over, Phase 1 clinical trials performed in 24 subjects, and showing favourable effects on body weight without central side effects [98]. LH-21 (CSIC, Madrid) and URB 447 (Piomelli, Tarzia Labs) are putative peripherally restricted CB1r antagonists that have shown positive effects in achieving weight loss and in reducing food intake in rodents, however, their mechanism of action remains largely unexplained [99]. Other compounds targeting the peripheral CB1r are currently under evaluation [100].

Conclusions

The recent history of the pharmacotherapy for obesity has been marked by severe restrictions of the regulatory committees of the EMA and the FDA. At the time of this review, orlistat is the only antiobesity drug available both in Europe and US, with some other amphetamine derivatives still marketed in the US with severe restrictions. The research of new antiobesity drugs goes on and two main directions are now being pursued: on the one side, the politherapies, which have shown promising results in the management of obesity and related co-morbidities without serious adverse events; on the other side, the targeted monotherapies, which seem to provide an intriguing way forward to fight obesity, even if positive results on humans have yet to be demonstrated. In conclusion, considering the complexity of the net of mechanisms that regulate food intake, energy expenditure, and the inter-individual response to different drugs, it is strongly recommended that, in the future, patients are carefully examined before starting any specific therapy, so that this is tailored to respond to their specific need and condition.

Conflict of interest The authors declare no conflict of interests.

References

1. WHO Library Cataloguing-in-Publication Data, Surveillance of chronic disease: risk factors: country-level data and comparable estimates (SuRF reports; 2), https://apps.who.int/infobase/Publicfiles/SuRF2.pdf
2. C.L. Ogden, M.D. Carroll, B.K. Kit, K.M. Flegal, Prevalence of obesity in the United States, 2009–2010. NCHS Data Brief **82**, 1–8 (2012)
3. European Commission, Eurostat, Overweight and obesity—BMI statistics (2011), http://epp.eurostat.ec.europa.eu/statistics_explained/index.php/Overweight_and_obesity_-_BMI_statistics
4. International Association for the Study of Obesity (IASO), http://www.iaso.org/
5. E.S. Leblanc, E. O'Connor, E.P. Whitlock, C.D. Patnode, T. Kapka, Effectiveness of primary care-relevant treatments for obesity in adults: a systematic evidence review for the U.S. Preventive Services Task Force. Ann. Intern. Med. **155**, 434–447 (2011)
6. R. Estruch, E. Ros, J. Salas-Salvadó, M.I. Covas, D. Pharm, D. Corella, F. Arós, E. Gómez-Gracia, V. Ruiz-Gutiérrez, M. Fiol, J. Lapetra, R.M. Lamuela-Raventos, L. Serra-Majem, X. Pintó, J. Basora, M.A. Muñoz, J.V. Sorlí, J.A. Martínez, M.A. Martínez-González, The PREDIMED Study Investigators, Primary prevention of cardiovascular disease with a Mediterranean diet. N. Engl. J. Med. **368**, 1279–1290 (2013)
7. J.L. Colquitt, J. Picot, E. Loveman, A.J. Clegg, Surgery for obesity. Cochrane Database Syst. Rev. **15**, CD003641 (2009)
8. L. Sjöström, A.K. Lindroos, M. Peltonen, J. Torgerson, C. Bouchard, B. Carlsson, S. Dahlgren, B. Larsson, K. Narbro, C.D. Sjöström, M. Sullivan, H. Wedel, Swedish Obese Subjects Study Scientific Group, Lifestyle, diabetes, and cardiovascular risk factors 10 years after bariatric surgery. N. Engl. J. Med. **351**, 2683–2693 (2004)
9. L. Sjöström, Review of the key results from the Swedish Obese Subjects (SOS) trial—a prospective controlled intervention study of bariatric surgery. J. Intern. Med. **273**, 219–234 (2013)
10. L. Sjöström, A. Gummesson, C.D. Sjöström, K. Narbro, M. Peltonen, H. Wedel, C. Bengtsson, C. Bouchard, B. Carlsson, S. Dahlgren, P. Jacobson, K. Karason, J. Karlsson, B. Larsson, A.K. Lindroos, H. Lönroth, I. Näslund, T. Olbers, K. Stenlöf, J. Torgerson, L.M. Carlsson, Swedish Obese Subjects Study, Effects of bariatric surgery on cancer incidence in obese patients in Sweden (Swedish Obese Subjects Study): a prospective, controlled intervention trial. Lancet Oncol. **10**, 653–662 (2009)
11. L. Sjöström, K. Narbro, C.D. Sjöström, K. Karason, B. Larsson, H. Wedel, T. Lystig, M. Sullivan, C. Bouchard, B. Carlsson, C. Bengtsson, S. Dahlgren, A. Gummesson, P. Jacobson, J. Karlsson, A.K. Lindroos, H. Lönroth, I. Näslund, T. Olbers, K. Stenlöf, J. Torgerson, G. Agren, L.M. Carlsson, Swedish Obese Subjects Study, Effects of bariatric surgery on mortality in Swedish obese subjects. N. Engl. J. Med. **357**, 741–752 (2007)
12. C. Gazzaruso, S. Giordanetti, A. La Manna, M. Celsa, E. De Amici, C. Turpini, A. Catona, P. Fratino, Weight loss after Swedish Adjustable Gastric Banding: relationships to insulin resistance and metabolic syndrome. Obes. Surg. **12**, 841–845 (2002)
13. A.P. Shukla, S.M. Ahn, R.T. Patel, M.W. Rosenbaum, F. Rubino, Surgical treatment of type 2 diabetes: the surgeon perspective. Endocrine **40**, 151–161 (2011)
14. B. Laferrère, Do we really know why diabetes remits after gastric bypass surgery? Endocrine **40**, 162–167 (2011)
15. K. Sjöholm, A. Anveden, M. Peltonen, P. Jacobson, S. Romeo, P.A. Svensson, L. Sjöström, L.M. Carlsson, Evaluation of Current Eligibility Criteria for Bariatric Surgery: diabetes prevention and risk factor changes in the Swedish Obese Subjects (SOS) study. Diabetes Care **36**(5), 1335–1340 (2013)
16. M. Fried, V. Hainer, A. Basdevant, H. Buchwald, M. Deitel, N. Finer, J.W. Greve, F. Horber, E. Mathus-Vliegen, N. Scopinaro, R. Steffen, C. Tsigos, R. Weiner, K. Widhalm, Interdisciplinary

European guidelines on surgery of severe obesity. Obes. Facts **1**, 52–59 (2008)
17. J.B. Dixon, P. Zimmet, K.G. Alberti, F. Rubino, Bariatric surgery: an IDF statement for obese Type 2 diabetes. Diabet. Med. **28**, 628–642 (2011)
18. G. Bray, *The battle of the bulge: a history of obesity research* (Dorrance Publishing Co., Pittsburg, 2007)
19. R.B. McFee, T.R. Caraccio, M.A. McGuigan, S.A. Reynolds, P. Bellanger, Dying to be thin: a dinitrophenol related fatality. Vet. Hum. Toxicol. **46**, 251–254 (2004)
20. L. Phillips, M.A. Singer, Peripheral neuropathy due to dinitrophenol used for weight loss: something old, something new. Neurology **80**, 773–774 (2013)
21. G. Glazer, Long-term pharmacotherapy of obesity 2000: a review of efficacy and safety. Arch. Intern. Med. **161**, 1814–1824 (2001)
22. Z. Li, M. Maglione, W. Tu, W. Mojica, D. Arterburn, L.R. Shugarman, L. Hilton, M. Suttorp, V. Solomon, P.G. Shekelle, S.C. Morton, Meta-analysis: pharmacologic treatment of obesity. Ann. Intern. Med. **142**, 532–546 (2005)
23. J.G. Kang, C.Y. Park, J.H. Kang, Y.W. Park, S.W. Park, Randomized controlled trial to investigate the effects of a newly developed formulation of phentermine diffuse-controlled release for obesity. Diabetes Obes. Metab. **12**, 876–882 (2010)
24. C.K. Haddock, W.S. Poston, P.L. Dill, J.P. Foreyt, M. Ericsson, Pharmacotherapy for obesity: a quantitative analysis of four decades of published randomized clinical trials. Int. J. Obes. Relat. Metab. Disord. **26**, 262–273 (2002)
25. C. Cercato, V.A. Roizenblatt, C.C. Leanca, A. Segal, A.P. Lopes Filho, M.C. Mancini, A. Halpern, A randomized double-blind placebo-controlled study of the long-term efficacy and safety of diethylpropion in the treatment of obese subjects. Int. J. Obes. (Lond.) **33**, 857–865 (2009)
26. F. Brenot, P. Herve, P. Petitpretz, F. Parent, P. Duroux, G. Simonneau, Primary pulmonary hypertension and fenfluramine use. Br. Heart J. **70**, 537–541 (1993)
27. J. McMurray, P. Bloomfield, H.C. Miller, Irreversible pulmonary hypertension after treatment with fenfluramine. BMJ **292**, 239–240 (1986)
28. J.G. Kang, C.Y. Park, Anti-obesity drugs: a review about their effects and safety. Diabetes Metab. J. **36**, 13–25 (2012)
29. H.M. Connolly, J.L. Crary, M.D. McGoon, D.D. Hensrud, B.S. Edwards, W.D. Edwards, H.V. Schaff, Valvular heart disease associated with fenfluramine–phentermine. N. Engl. J. Med. **337**, 581–588 (1997)
30. D. Rucker, R. Padwal, S.K. Li, C. Curioni, D.C. Lau, Long term pharmacotherapy for obesity and overweight: updated meta-analysis. BMJ **335**, 1194–1199 (2007)
31. O. Bosello, M.O. Carruba, E. Ferrannini, C.M. Rotella, Sibutramine lost and found. Eat. Weight Disord. **7**, 161–167 (2002)
32. European Medicine Agency (EMA), Opinion following an Article 31 referral for Sibutramine International Non-Proprietary Name (INN): Sibutramine: Background information and Annexes I, II, III. EMA website, http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Sibutramine_31/WC500013923.pdf
33. W.P.T. James, I.D. Caterson, W. Coutinho, N. Finer, L.F. Van Gaal, A.P. Maggioni, C. Torp-Pedersen, A.M. Sharma, G.M. Shepherd, R.A. Rode, C.L. Renz, SCOUT Investigators, Effect of sibutramine on cardiovascular outcomes in overweight and obese subjects. N. Engl. J. Med. **363**, 905–917 (2010)
34. European Medicine Agency (EMA), Questions and answers on the suspension of medicines containing sibutramine. EMA website, http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Sibutramine_107/WC500094238.pdf
35. US Department of Health and Human Services, Food and Drug Administration (FDA), FDA Drug Safety Communication: FDA recommends against the continued use of meridia (sibutramine). FDA website, http://www.fda.gov/Drugs/DrugSafety/ucm228746.htm
36. C. Quarta, R. Mazza, S. Obici, R. Pasquali, U. Pagotto, Energy balance regulation by endocannabinoids at central and peripheral levels. Trends Mol. Med. **17**, 518–526 (2011)
37. G. Colombo, R. Agabio, G. Diaz, C. Lobina, R. Reali, G.L. Gessa, Appetite suppression and weight loss after the cannabinoid antagonist SR 141716. Life Sci. **63**, 113–117 (1998)
38. L.F. Van Gaal, A.M. Rissanen, A.J. Scheen, O. Ziegler, S. Rössner, RIO-Europe Study Group, Effects of the cannabinoid-1 receptor blocker rimonabant on weight reduction and cardiovascular risk factors in overweight patients: 1-year experience from the RIO-Europe study. Lancet **365**, 1389–1397 (2005)
39. F.X. Pi-Sunyer, L.J. Aronne, H.M. Heshmati, J. Devin, J. Rosenstock, RIO-North America Study Group, Effect of rimonabant, a cannabinoid-1 receptor blocker, on weight and cardiometabolic risk factors in overweight or obese patients: RIO-North America: a randomized controlled trial. JAMA **295**, 761–775 (2006)
40. L.F. Van Gaal, A.J. Scheen, A.M. Rissanen, S. Rössner, C. Hanotin, O. Ziegler, RIO-Europe Study Group, Long-term effect of CB1 blockade with rimonabant on cardiometabolic risk factors: two year results from the RIO-Europe Study. Eur. Heart J. **29**, 1761–1771 (2008)
41. A.J. Scheen, N. Finer, P. Hollander, M.D. Jensen, L.F. Van Gaal, RIO-Diabetes Study Group, Efficacy and tolerability of rimonabant in overweight or obese patients with type 2 diabetes: a randomised controlled study. Lancet **368**, 1660–1672 (2006)
42. J. Rosenstock, P. Hollander, S. Chevalier, A. Iranmanesh, SERENADE Study Group, SERENADE: the Study Evaluating Rimonabant Efficacy in Drug-naive Diabetic Patients: effects of monotherapy with rimonabant, the first selective CB1 receptor antagonist, on glycemic control, body weight, and lipid profile in drug-naive type 2 diabetes. Diabetes Care **31**, 2169–2176 (2008)
43. J.P. Després, A. Golay, L. Sjöström, Rimonabant in Obesity-Lipids Study Group, Effects of rimonabant on metabolic risk factors in overweight patients with dyslipidemia. N. Engl. J. Med. **353**, 2121–2134 (2005)
44. R. Christensen, P.K. Kristensen, E.M. Bartels, H. Bliddal, A. Astrup, Efficacy and safety of the weight-loss drug rimonabant: a meta-analysis of randomised trials. Lancet **370**, 1706–1713 (2007)
45. European Medicine Agency (EMA), Public statement on Acomplia (rimonabant). EMA website, http://www.ema.europa.eu/docs/en_GB/document_library/Public_statement/2009/11/WC500012189.pdf
46. E.J. Topol, M.G. Bousser, K.A. Fox, M.A. Creager, J.P. Despres, J.D. Easton, C.W. Hamm, G. Montalescot, P.G. Steg, T.A. Pearson, E. Cohen, C. Gaudin, B. Job, J.H. Murphy, D.L. Bhatt, CRESCENDO Investigators, Rimonabant for prevention of cardiovascular events (CRESCENDO): a randomised, multicentre, placebo-controlled trial. Lancet **376**, 517–523 (2010)
47. J.E. Boesten, J. Kaper, H.E. Stoffers, A.A. Kroon, O.C. van Schayck, Rimonabant improves obesity but not the overall cardiovascular risk and quality of life; results from CARDIO-REDUSE (CArdiometabolic Risk reDuctIOn by Rimonabant: the Effectiveness in Daily practice and its USE). Fam. Pract. **29**, 521–527 (2012)
48. B. Borgstrom, Mode of action of tetrahydrolipstatin: a derivative of the naturally occurring lipase inhibitor lipstatin. Biochim. Biophys. Acta **962**, 308–316 (1988)
49. S. Rossner, L. Sjostrom, R. Noack, A.E. Meinders, G. Noseda, European Orlistat Obesity Study Group, Weight loss, weight maintenance, and improved cardiovascu-lar risk factors after

2 years treatment with orlistat for obesity. Obes. Res. **8**, 49–61 (2000)
50. J.S. Torgerson, J. Hauptman, M.N. Boldrin, L. Sjostrom, XENical in the prevention of diabetes in obese subjects (XENDOS) study: a randomized study of orlistat as an adjunct to lifestyle changes for the prevention of type 2 diabetes in obese patients. Diabetes Care **27**, 155–161 (2004)
51. US Department of Health and Human Services, Food and Drug Administration (FDA), Questions and answers: orlistat and severe liver injury. FDA drug bulletin, 26 May 2010. FDA website, http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationfor PatientsandProviders/ucm213040.htm
52. M.A. Weir, M.M. Beyea, T. Gomes, D.N. Juurlink, M. Mamdani, P.G. Blake, R. Wald, A.X. Garg, Orlistat and acute kidney injury: an analysis of 953 patients. Arch. Intern. Med. **171**, 703–704 (2011)
53. K.M. Gadde, D.B. Allison, D.H. Ryan, C.A. Peterson, B. Troupin, M.L. Schwiers, W.W. Day, Effects of low-dose, controlled-release, phentermine plus topiramate combination on weight and associated comorbidities in overweight and obese adults (CONQUER): a randomised, placebo-controlled, phase 3 trial. Lancet **377**, 1341–1352 (2011)
54. M.H. Davidson, S. Tonstad, S. Oparil, M. Schwiers, W.W. Day, C.H. Bowden, Changes in cardiovascular risk associated with phentermine and topiramate extended-release in participants with comorbidities and a body mass index ≥27 kg/m(2). Am. J. Cardiol. (2013). doi:10.1016/j.amjcard.2012.12.038
55. European Medicine Agency (EMA), Questions and answers on the refusal of the marketing authorisation for Qsiva (phentermine/topiramate). EMA website, http://www.ema.europa.eu/docs/en_GB/document_library/Summary_of_opinion_-_Initial_authorisation/human/002350/WC500134085.pdf
56. US Department of Health and Human Services, Food and Drug Administration (FDA). FDA website, http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/022580s001lbl.pdf
57. US Department of Health and Human Services, Food and Drug Administration (FDA), Guidance for industry. Developing products for weight management. FDA website, http://www.fda.gov/downloads/Drugs/.../Guidances/ucm071612.pdf
58. European Medicine Agency (EMA), Committee for Medicinal Products for Human use (CHMP), Guideline on clinical investigation of medicinal products used in weight control. EMA website, http://www.emea.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003213.pdf
59. A.B. Goldfine, Assessing the cardiovascular safety of diabetes therapies. N. Engl. J. Med. **359**, 1092–1095 (2008)
60. US Department of Health and Human Services, Food and Drug Administration (FDA), Briefing information for the March 28–29, 2012 Meeting of the Endocrinological and Metabolic Drug Advisory Committee. FDA website, http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/ucm297239.htm
61. D.D. Lam, M.J. Przydzial, S.H. Ridley, G.S. Yeo, J.J. Rochford, S. O'Rahilly, L.K. Heisler, Serotonin 5-HT2C receptor agonist promotes hypophagia via downstream activation of melanocortin 4 receptors. Endocrinology **149**, 1323–1328 (2008)
62. Y. Xu, J.E. Jones, D. Kohno, K.W. Williams, C.E. Lee, M.J. Choi, J.G. Anderson, L.K. Heisler, J.M. Zigman, B.B. Lowell, J.K. Elmquist, 5-HT2CRs expressed by pro-opiomelanocortin neurons regulate energy homeostasis. Neuron **60**, 582–589 (2008)
63. US Department of Health and Human Services, Food and Drug Administration (FDA), FDA approves Belviq to treat some overweight or obese adults. FDA website, http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm309993.htm?utm_source=twitterfeed%26utm_medium=twitter
64. S.R. Smith, N.J. Weissman, C.M. Anderson, M. Sanchez, E. Chuang, S. Stubbe, H. Bays, W.R. Shanahan, Behavioral Modification and Lorcaserin for Overweight and Obesity Management (BLOOM) Study Group, Multicenter, placebo-controlled trial of lorcaserin for weight management. N. Engl. J. Med. **363**, 245–256 (2010)
65. M.C. Fidler, M. Sanchez, B. Raether, N.J. Weissman, S.R. Smith, W.R. Shanahan, C.M. Anderson, BLOSSOM Clinical Trial Group, A one-year randomized trial of lorcaserin for weight loss in obese and overweight adults: the BLOSSOM trial. J. Clin. Endocrinol. Metab. **96**, 3067–3077 (2011)
66. P.M. O'Neil, S.R. Smith, N.J. Weissman, M.C. Fidler, M. Sanchez, J. Zhang, B. Raether, C.M. Anderson, W.R. Shanahan, Randomized placebo-controlled clinical trial of lorcaserin for weight loss in type 2 diabetes mellitus: the BLOOM-DM study. Obesity (Silver Spring) **20**, 1426–1436 (2012)
67. E.W. Chan, Y. He, C.S. Chui, A.Y. Wong, W.C. Lau, I.C. Wong, Efficacy and safety of lorcaserin in obese adults: a meta-analysis of 1-year randomized controlled trials (RCTs) and narrative review on short-term RCTs. Obes. Rev. (2013). doi: 10.1111/obr.12015
68. European Medicine Agency (EMA), Pharmacovigilance Risk Assessment Committee (PRAC). Draft agenda of meeting 7–10 Jan 2013. EMA website, http://www.ema.europa.eu/docs/en_GB/document_library/Agenda/2013/01/WC500137109.pdf
69. S. Madsbad, Treatment of type 2 diabetes with incretin-based therapies. Lancet **373**, 438–439 (2009)
70. A. Astrup, R. Carraro, N. Finer, A. Harper, M. Kunesova, M.E. Lean, L. Niskanen, M.F. Rasmussen, A. Rissanen, S. Rössner, M.J. Savolainen, L. Van Gaal, Safety, tolerability and sustained weight loss over 2 years with the once-daily human GLP-1 analog, liraglutide. Int. J. Obes. (Lond.) (2013). doi:10.1038/ijo.2012.19236
71. A. Astrup, S. Rössner, L. Van Gaal, A. Rissanen, L. Niskanen, M. Al Hakim, J. Madsen, M.F. Rasmussen, M.E. Lean, NN8022-1807 Study Group, Effects of liraglutide in the treatment of obesity: a randomised, double-blind, placebo-controlled study. Lancet **374**, 1606–1616 (2009)
72. J.B. Buse, M. Nauck, T. Forst, W.H. Sheu, S.K. Shenouda, C.R. Heilmann, B.J. Hoogwerf, A. Gao, M.K. Boardman, M. Fineman, L. Porter, G. Schernthaner, Exenatide once weekly versus liraglutide once daily in patients with type 2 diabetes (DURATION-6): a randomised, open-label study. Lancet **381**, 117–124 (2013)
73. S.S. Torekov, S. Madsbad, J.J. Holst, Obesity—an indication for GLP-1 treatment? Obesity pathophysiology and GLP-1 treatment potential. Obes. Rev. **12**, 593–601 (2011)
74. K.M. Gadde, D.M. Franciscy, H.R. Wagner 2nd, K.R. Krishnan, Zonisamide for weight loss in obese adults: a randomized controlled trial. JAMA **289**, 1820–1825 (2003)
75. N.T. Bello, M.R. Zahner, Tesofensine, a monoamine reuptake inhibitor for the treatment of obesity. Curr. Opin. Investig. Drugs **10**, 1105–1116 (2009)
76. A. Sjödin, C. Gasteyger, A.L. Nielsen, A. Raben, J.D. Mikkelsen, J.K. Jensen, D. Meier, A. Astrup, The effect of the triple monoamine reuptake inhibitor tesofensine on energy metabolism and appetite in overweight and moderately obese men. Int. J. Obes. (Lond.) **34**, 1634–1643 (2010)
77. A. Astrup, S. Madsbad, L. Breum, T.J. Jensen, J.P. Kroustrup, T.M. Larsen, Effect of tesofensine on bodyweight loss, body composition, and quality of life in obese patients: a randomised, double-blind, placebo-controlled trial. Lancet **372**, 1906–1913 (2008)

78. S.A. Doggrell, Tesofensine—a novel potent weight loss medicine. Evaluation of: Astrup A, Breum L, Jensen TJ, Kroustrup JP, Larsen TM. Effect of tesofensine on bodyweight loss, body composition, and quality of life in obese patients: a randomised, double-blind, placebo-controlled trial. Expert Opin. Investig. Drugs **18**, 1043–1046 (2009)
79. R.A.H. Adan, L.J.M.J. Vandershuren, S.E. la Fleur, Anti-obesity drugs and neural circuits of feeding. Trends Pharmacol. Sci. **29**, 208–217 (2008)
80. F.L. Greenway, M.J. Whitehouse, M. Guttadauria, J.W. Anderson, R.L. Atkinson, K. Fujioka, K.M. Gadde, A.K. Gupta, P. O'Neil, D. Schumacher, D. Smith, E. Dunayevich, G.D. Tollefson, E. Weber, M.A. Cowley, Rational design of a combination medication for the treatment of obesity. Obesity (Silver Spring) **17**, 30–39 (2009)
81. F.L. Greenway, K. Fujioka, R.A. Plodkowski, S. Mudaliar, M. Guttadauria, J. Erickson, D.D. Kim, E. Dunayevich, COR-I Study Group, Effect of naltrexone plus bupropion on weight loss in overweight and obese adults (COR-I): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. Lancet **376**, 595–605 (2010)
82. T.A. Wadden, J.P. Foreyt, G.D. Foster, J.O. Hill, S. Klein, P.M. O'Neil, M.G. Perri, F.X. Pi-Sunyer, C.L. Rock, J.S. Erickson, H.N. Maier, D.D. Kim, E. Dunayevich, Weight loss with naltrexone SR/bupropion SR combination therapy as an adjunct to behavior modification: the COR-BMOD trial. Obesity (Silver Spring) **19**, 110–120 (2011)
83. C. Apovian, L. Aronne, D. Rubino, C. Still, H. Wyatt, C. Burns, D. Kim, E. Dunayevich, COR-II Study Group, A randomized, phase 3 Trial of naltrexone SR/Bupropion SR on weight and obesity-related risk factors (COR-II). Obesity (Silver Spring) (2013). doi:10.1002/oby.20309
84. US National Institute of Health (NIH), http://clinicaltrials.gov/ct2/show/record/NCT00474630?term=contrave&rank=4
85. Orexigen® Press Release, http://ir.orexigen.com/phoenix.zhtml?c=207034&p=irol-newsArticle_pf&id=1441827
86. US Department of Health and Human Services, Food and Drug Administration (FDA), FDA briefing document. FDA website, http://www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/endocrinologicandmetabolicdrugsadvisorycommittee/ucm235671.pdf
87. US National Institute of Health (NIH), http://clinicaltrials.gov/ct2/show/NCT01601704?term=contrave&rank=3
88. K.M. Gadde, G.M. Yonish, M.S. Foust, H.R. Wagner, Combination therapy of zonisamide and bupropion for weight reduction in obese women: a preliminary, randomized, open-label study. J. Clin. Psychiatry **68**, 1226–1229 (2007)
89. L.L. Ioannides-Demos, L. Piccenna, J.J. McNeil, Pharmacotherapies for obesity: past, current, and future therapies. J. Obes. (2011). doi:10.1155/2011/179674
90. Orexigen® Press Release. San Diego, 9 May 2012, http://ir.orexigen.com/phoenix.zhtml?c=207034&p=irol-newsArticle_print&ID=1694059&highlight=
91. J.W. Day, N. Ottaway, J.T. Patterson, V. Gelfanov, D. Smiley, J. Gidda, H. Findeisen, D. Bruemmer, D.J. Drucker, N. Chaudhary, J. Holland, J. Hembree, W. Abplanalp, E. Grant, J. Ruehl, H. Wilson, H. Kirchner, S.H. Lockie, S. Hofmann, S.C. Woods, R. Nogueiras, P.T. Pfluger, D. Perez-Tilve, R. DiMarchi, M.H. Tschöp, A new glucagon and GLP-1 co-agonist eliminates obesity in rodents. Nat. Chem. Biol. **5**, 749–757 (2009)
92. R.E. Steinert, C. Feinle-Bisset, N. Geary, C. Beglinger, Secretion of gastrointestinal hormones and eating control. J. Anim. Sci. (2013) [Epub ahead of print]
93. Society for Endocrinology Media Release, Society for Endocrinology website. Hormone combination shows promise in the treatment of obesity and diabetes, http://www.endocrinology.org/press/pressreleases/2013-03-19_GLP1glucagonCombo_SfEBES2013conferencePressRelease.pdf
94. Y. Xu, T.P. Nedungadi, L. Zhu, N. Sobhani, B.G. Irani, K.E. Davis, X. Zhang, F. Zou, L.M. Gent, L.D. Hahner, S.A. Khan, C.F. Elias, J.K. Elmquist, D.J. Clegg, Distinct hypothalamic neurons mediate estrogenic effects on energy homeostasis and reproduction. Cell Metab. **14**, 453–465 (2011)
95. B. Finan, B. Yang, N. Ottaway, K. Stemmer, T.D. Müller, C.X. Yi, K. Habegger, S.C. Schriever, C. García-Cáceres, D.G. Kabra, J. Hembree, J. Holland, C. Raver, R.J. Seeley, W. Hans, M. Irmler, J. Beckers, M.H. de Angelis, J.P. Tiano, F. Mauvais-Jarvis, D. Perez-Tilve, P. Pfluger, L. Zhang, V. Gelfanov, R.D. DiMarchi, M.H. Tschöp, Targeted estrogen delivery reverses the metabolic syndrome. Nat. Med. **18**, 1847–1856 (2012)
96. C. Quarta, L. Bellocchio, G. Mancini, R. Mazza, C. Cervino, L.J. Braulke, C. Fekete, R. Latorre, C. Nanni, M. Bucci, L.E. Clemens, G. Heldmaier, M. Watanabe, T. Leste-Lassere, M. Maitre, L. Tedesco, F. Fanelli, S. Reuss, S. Klaus, R.K. Srivastava, K. Monory, A. Valerio, A. Grandis, R. De Giorgio, R. Pasquali, E. Nisoli, D. Cota, B. Lutz, G. Marsicano, U. Pagotto, CB(1) signaling in forebrain and sympathetic neurons is a key determinant of endocannabinoid actions on energy balance. Cell Metab. **11**, 273–285 (2010)
97. J. Tam, V.K. Vemuri, J. Liu, S. Bátkai, B. Mukhopadhyay, G. Godlewski, D. Osei-Hyiaman, S. Ohnuma, S.V. Ambudkar, J. Pickel, A. Makriyannis, G. Kunos, Peripheral CB1 cannabinoid receptor blockade improves cardiometabolic risk in mouse models of obesity. J. Clin. Invest. **120**, 2953–2966 (2010)
98. 7TM Pharma, 7TM Pharma successfully conducts clinical Phase I trial of its first in class peripheral CB1 receptor antagonist TM38837 demonstrating restriction from the human CNS, http://7tm.com/News.aspx?M=News&PID=5&NewsID=58. Accessed 17 Nov 2010
99. S.J. Ward, R.B. Raffa, Rimonabant redux and strategies to improve the future outlook of CB1 receptor neutral-antagonist/inverse-agonist therapies. Obesity (Silver Spring) **19**, 1325–1334 (2011)
100. E. Kirilly, X. Gonda, G. Bagdy, CB1 receptor antagonists: new discoveries leading to new perspectives. Acta Physiol. **205**, 41–60 (2012)