Anti-obesity drugs: a review about their effects and their safety

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Introduction: Amphetamines, rimonabant and sibutramine licenses as anti-obesity drugs have been withdrawn because of their adverse effects. In fact, orlistat is the only available long-term treatment for obesity.

Areas covered: The efficacy and safety of long-term drug therapy is very important in the management obesity; for this reason, the authors decided to conduct a review on the efficacy and safety of current, past and future pharmacotherapies for weight loss.

Expert opinion: Orlistat is a good choice for the treatment of obesity, because of its safety on cardiovascular events and its positive effects on diabetic control, even if it is not as effective as rimonabant or sibutramine in reducing body weight. Regarding emerging anti-obesity therapies in diabetic people, we currently have drugs that have already been marketed including the glucagon-like peptide-1 (GLP-1) receptor agonists exenatide and liraglutide; other than improving glycemic control, they also suppress appetite reducing body weight. Moreover, some other drugs are currently in study such as tesofensine, phentermine + topiramate, bupropion + naltrexone and bupropion + zonisamide. Furthermore, several additional gut hormone-based treatments for obesity are under investigation in Phase II and III clinical trials, with particular focus on ghrelin, peptide YY, pancreatic polypeptide, amylin and oxyntomodulin.

Keywords: emerging therapy, obesity management, orlistat, rimonabant, sibutramine

1. Introduction

Obesity, defined as a body mass index (BMI) of ≥ 30 kg/m², has reached epidemic proportions worldwide, with an estimated 97 million adults in the USA overweight or obese [1]. Obesity substantially raises the risk of morbidity from dyslipidemia [2], type 2 diabetes mellitus (T2DM) [3], fatty liver [4], coronary heart disease and stroke [5], hypertension, gallbladder disease, osteoarthritis, sleep apnea and respiratory problems, endometrial, breast, prostate and colon cancers [6]. The current recommendations for the treatment of overweight and obese people include increased physical activity and reduced calorie intake [7,8]; when the behavioral approach is not sufficient to get the optimal target of weight and metabolic control, a pharmacologic treatment is recommended [9].

Usually weight loss medications are recommended for patients with a BMI ≥ 30 kg/m², as well as for those with a BMI ≥ 27 kg/m² and a weight-related comorbidity [10]. In the last years, a lot of drugs have been marketed and then lately withdrawn due to serious adverse events. The only anti-obesity medication approved for long-term treatment of obesity is orlistat [11]; in the USA, other than orlistat, phentermine is also available, but only for short term use (≤ 12 weeks).
Article highlights.

- Obesity has reached epidemic proportions worldwide, with an estimated 97 million adults in the USA who are overweight or obese.
- In the past years, a lot of molecules have been approved for the treatment of obesity, but a lot of them (amphetamine, sibutramine, rimonabant) have been withdrawn from the market because of their adverse effects.
- Even if orlistat is not as effective as the other drugs in reducing body weight, it is the only available choice at the moment for the treatment of obesity, because of its safety on cardiovascular events and its positive effects on diabetic control.
- In a particular population, such as diabatic people, we currently have some already marketed drugs, glucagon-like peptide-1 (GLP-1) receptor agonists (exenatide and liraglutide) that can be useful also for the treatment of obesity.
- Some other drugs are currently in study to be approved as anti-obesity drugs such as tesofensine, an association of phentermine and topiramate, a combination of bupropion and naltrexone and an association of bupropion and zonisamide. Moreover, several gut hormone-based treatments for obesity are under investigation in Phase II and III clinical trials.

1.1 History

Between the 1930s and the present, more than a half dozen drugs were widely prescribed to obese patients for a period, then later removed from the market due to the serious adverse events. The first attempt to develop an anti-obesity drug can be dated to 1800s, when, based on its effectiveness for hypothyroidism, thyroid hormone became a popular treatment for obesity in euthyroid people. It had a modest effect, but produced the symptoms of hyperthyroidism as a side effect, such as palpitations and difficulty sleeping. Dinitrophenol was introduced in 1933; this worked by uncoupling the biological process of oxidative phosphorylation in mitochondria, causing them to produce heat instead of ATP. The most significant side effect was a sensation of warmth, frequently with sweating. Overdose, although rare, lead to a rise in body temperature and, ultimately, fatal hyperthermia. By the end of 1938, dinitrophenol had fallen out of use, because the FDA had become empowered to put pressure on manufacturers, who voluntarily withdrew it from the market [10]. Amphetamines became popular for weight loss during the late 1930s as the short-term treatment of obesity (≤ 12 weeks). They worked primarily by suppressing appetite, and had other beneficial effects such as increased alertness. Unfortunately, amphetamines elevate cardiac output, and blood pressure making it dangerous for use by patients with a history of heart disease or hypertension. Moreover, tolerance is developed rapidly in amphetamine abuse; therefore, periods of extended use require increasing amounts of the drug in order to achieve the same effect. Abuse of amphetamines can result in a stimulant psychosis that can present as a number of psychotic disorders. For all these reasons, and the adding risk of serious adverse events, such as pulmonary hypertension, amphetamines were withdrawn from the European market in 1979, while they were maintained in America. In 1967/1968, a number of deaths attributed to diet pills triggered a Senate investigation and the gradual implementation of greater restrictions on the market. This culminating with the Food and Drug Administration (FDA) banning the use of amphetamines, then the most effective of the diet drugs, in diet pills [12]. Meanwhile, phentermine had been approved by the FDA in 1959 and fenfluramine in 1973. Dexfenfluramine was developed in the mid-1990s as an alternative to fenfluramine with less side effects, and received regulatory approval in 1996. These drugs were no more popular than other drugs until a researcher reported that the association of phentermine with fenfluramine or dexfenfluramine caused a 10% weight loss which was maintained for more than 2 years [12]. An association of the two drugs was created and rapidly became the most commonly prescribed diet medication; however, this coincided with mounting evidence that the combination could cause valvular heart disease in up to 30% of those who had taken it, leading to withdrawal of fenfluramine and dexfenfluramine from the market in September 1997, while the FDA did not ask manufacturers to remove phentermine from the market and phentermine is still available by itself in most countries [13]. In 1997, sibutramine (5, 10 and 15 mg) was approved by the FDA for the management of obesity, including weight loss and maintenance of weight loss, in conjunction with a reduced calorie diet, and have been authorized in the European Union (EU) since 1999. Sibutramine hydrochloride monohydrate is a norepinephrine and serotonin reuptake inhibitor. Sibutramine is rapidly metabolized by the hepatic cytochrome P450 system generating two pharmacologic active metabolites which affect both food intake and energy expenditure [14]. Since sibutramine’s FDA approval in 1997, caution has been recommended in patients with poorly controlled hypertension or a history of coronary artery disease, stroke or arrhythmia because of increases in systolic blood pressure (SBP) and diastolic blood pressure (DBP) and pulse caused by the drug. However, after the data from the Sibutramine Cardiovascular Outcomes Trial (SCOUT) were published [15], sibutramine was withdrawn due to cardiovascular concerns first in Europe, in August 2010 [16], and then in the USA and Canadian markets, in October 2010 [17]. The data from the SCOUT study showed a 16% rise in the risk of non-fatal myocardial infarction or stroke in people taking sibutramine. Rimonabant had been approved in Europe in 2006 for the treatment of obesity; while it did not receive approval in the USA or Canada due to safety concerns. Rimonabant is a cannabinoid receptor antagonist that acts by blocking cannabinoid type 1 (CB1) receptors that are found in the nervous system and are part of the system that the body uses to control
food intake. By blocking the receptors, rimonabant can help patients to reduce food intake and to lose weight [18]. Despite its positive effects on body weight, the European Medicines Agency (EMEA) in October 2008 recommended the suspension of the sale of rimonabant as the risks seem to be greater than the benefits due to an approximate doubling of the risk of psychiatric disorders [19,20]. Actually the only anti-obesity medication currently approved by the EMEA in Europe for long-term use is orlistat, while in the USA other orlistat phentermine is also available, but only for short-term use. In fact, although in Europe phentermine license was withdrawn in 1999, in America phentermine is an approved anti-obesity agent indicated as an adjunct to appropriate nutrition and physical exercise for short-term (up to 12 weeks) treatment of obesity.

The efficacy and safety of long-term drug therapy is a very important consideration in the management obesity which often requires ongoing therapy to achieve and maintain the weight loss. In line with a previously reported review [21], we decided to conduct a review on the efficacy and safety of current, past and future pharmacotherapies for weight loss.

2. Material and methods

A systematic search strategy was developed to identify randomized controlled trials in both MEDLINE (National Library of Medicine, Bethesda, MD; 1996 through March 2011) and the Cochrane Register of Controlled Trials (The Cochrane Collaboration, Oxford, UK). The terms ‘amphetamine’, ‘phentermine’, ‘rimonabant’, ‘sibutramine’ or ‘orlistat’, ‘body weight’, ‘adverse effects’, ‘cardiovascular events’, ‘anti-obesity drugs’, were incorporated into an electronic search strategy that included the Dickersin filter for randomized controlled trials [22]. The bibliographies of all identified randomized trials and review articles were reviewed to look for additional studies of interest. We reviewed all of the citations retrieved from the electronic search to identify potentially relevant articles for this review. We subsequently reviewed the potential trials to determine their eligibility. To qualify for inclusion, clinical trials were required to meet a series of predetermined criteria regarding study design, study population, interventions evaluated and outcome measured. Eligible trials had to present results on the variation of body weight. Two different outcomes related to body weight decrease were of primary interest: i) the proportion of individuals within each treatment group achieving clinically significant (> 5.0%) body weight reduction, and ii) the mean amount decrease of body weight within each treatment group. Variations of SBP, DBP, data on glycemic control, total cholesterol (TC), low-density lipoprotein-cholesterol (LDL-C), high-density lipoprotein-cholesterol (HDL-C) and triglycerides (Tg) that occurred during various trials were secondary outcomes of interest. The following data were abstracted onto standardized case report forms: authors; year of publication; country of study; source of funding; study goal; means of randomization and blinding; duration of treatment; treatment characteristics; sex; quantity of and reasons for study withdrawal; HbA1c and age characteristics of the treatment and control groups; outcomes and adverse event data. A validated, 3-item scale was used to evaluate the overall reporting quality of the trials selected for inclusion in the present review. This scale provided scoring for randomization (0 – 2 points), double-blinding (0 – 2 points) and account for withdrawals (1 point). Scores ranged between 0 and 5, and scores 3 indicated a study of high quality [23], and study selection was restricted to randomized controlled trials to ensure the inclusion of only high quality evidence.

2.1 Mechanism of action, including key PK/PD data

2.1.1 Phentermine

Phentermine was first approved by the US FDA in 1959 [24], and due to its generic status, phentermine was the most commonly prescribed appetite suppressant [25]. Phentermine is an amphetamine analog stimulant approved for short-term use, because long-term clinical trials showed increased tolerance and dependency from its prolonged use [26,27]. This drug acts as sympathomimetic agents; the mechanism of action includes an increase in central nervous system dopamine and norepinephrine (both catecholamines), and serotonin (an indolamine) activity, resulting in appetite suppression. As stimulants, it also increases blood pressure and heart rate. Moreover, different clinical trials in humans suggest sympathomimetic agents increase energy expenditure [28,29].

Phentermine resin formulations allow for a slower gastrointestinal release after ingestion. Administration of phentermine resin often begins with a 15 mg dose, titrated to 30 mg/day if needed. In the 1970s, phentermine hydrochloride (HCl) was developed, with doses ranging from 8 to 37.5 mg, which is generally equivalent to 6.4 – 30 mg of phentermine resin. The phentermine HCl salt easily dissociates in the gastrointestinal tract, resulting in immediate release of phentermine drug; phentermine HCl is absorbed from the gastrointestinal tract approximately three times faster than phentermine resin [30]. Theoretically, immediate-release phentermine HCl has a more intense appetite suppressant effect compared with phentermine resin, but for a shorter duration of time.

Phentermine is contraindicated in patients with pulmonary artery hypertension, severe arterial hypertension, current or past medical history of cardiovascular or cerebrovascular disease or psychiatric disorders including anorexia and depression; it is also contraindicated in patients with propensity toward drug abuse or known alcoholism. Combination drug therapy with any other centrally acting anorectic agent is contraindicated due to the increased risk of potentially fatal pulmonary artery hypertension.

2.1.2 Sibutramine

Sibutramine hydrochloride monohydrate is a norepinephrine and serotonin reuptake inhibitor.
Sibutramine was approved by the FDA in 1997; in that same year, two other appetite-suppressant drugs with a similar mechanism of action, fenfluramine and dexfenfluramine, were removed from the market because of serious, unexpected cardiovascular adverse events, primary pulmonary hypertension and valvular regurgitation, which resulted in substantial morbidity and mortality [31]. Sibutramine is rapidly metabolized by the hepatic cytochrome P450 system generating two pharmacologic active metabolites which affect both food intake and energy expenditure [32]. Sibutramine is not available anymore since EMEA’s Committee before [16], and the FDA later [17], recommended its suspension in 2010 due to cardiovascular concern. In detail, the EMEA chose to suspend the drug because of the potential increased risk of heart attack and stroke in obese patients emerged after the publication of data from the SCOUT trial [15], for a marginal weight loss compared with placebo, and for a lack of data on weight loss maintenance after drug cessation [16].

2.1.3 Orlistat

Orlistat 120 mg was approved as a prescription product by the FDA in 1999 for obesity management in conjunction with a reduced caloric diet, and to reduce the risk of regaining weight after prior weight loss. In 2007, orlistat 60 mg was approved for an over-the-counter (OTC) use for weight loss in overweight adults, 18 years and older, in conjunction with a reduced-calorie and low-fat diet. Currently, orlistat is approved for marketing in approximately 100 countries. Orlistat is the first prescription treatment for obesity that does not act as an appetite suppressant, but it works by interfering with the action of gastrointestinal lipase in the gastrointestinal tract [33].

Orlistat has a unique molecular structure, which allows it to bind to the active site of gastrointestinal lipase and block that enzyme activity. The enzyme is thus unable to break Tg down into their component parts. As a result of this mechanism of action, 30% of ingested dietary fat remains undigested and unabsorbed, passing through the gastrointestinal tract unchanged. Orlistat treatment can cause mild to moderate gastrointestinal side effects that usually attenuate with the prosecution of the treatment [34], and some rare pharmacokinetic interactions with cyclosporin [35] and warfarin [36]. Orlistat is contraindicated in individuals with chronic malabsorption syndromes or cholestasis.

Orlistat is given as one capsule taken with water just before, during or up to 1 h after each main meal. If a meal is missed or contains no fat, orlistat should not be taken. The patient should be on a diet in which about 30% of the calories come from fat, and which is rich in fruit and vegetables. The food in the diet should be spread over three main meals. Treatment with orlistat should be stopped after 12 weeks if patients have been unable to lose at least 5% of their body weight since the start of treatment.

The most common side effects with orlistat are influenza, hypoglycemia, headache, upper respiratory infection, oily spotting from the rectum, abdominal pain or discomfort, flatus with discharge, fecal urgency, fatty or oily stools, flatulence, liquid stools, oily evacuation and increased defecation. These symptoms generally occur at the beginning of treatment, and go away after some time. Orlistat should not be used in people who may be hypersensitive to orlistat or any of the other ingredients. It should also not be used in people with a long-term malabsorption disease (where nutrients from the food are not easily absorbed during digestion), with cholestasis or who are breast-feeding. Moreover, recently, on June 2010, the FDA approved a revised label for orlistat to include new safety information about cases of severe liver injury that have been reported rarely with the use of this medication [37].

2.1.4 Rimonabant

Rimonabant is a cannabinoid receptor antagonist; it acts by blocking a specific type of receptor called CB1 receptors that are found in the nervous system and are part of the system that the body uses to control food intake. By blocking the receptors, rimonabant can help patients to reduce food intake and to lose weight [38]. The endogenous cannabinoid system governs, among other things, aspects of food intake and energy balance [39], making it an available target to curb appetite and to help reduce health concerns related to obesity. Several molecules targeting the cannabinoid system have been described, with the selective CB1 receptor antagonist/inverse agonist, rimonabant, exemplifying the most advanced and well-characterized compound to date [40]. In 2007, the cannabinoid receptor antagonist rimonabant was withdrawn by the FDA from the European market because of an increased risk of depression, anxiety and suicidal ideation [41].

3. Clinical applications, including key efficacy data

3.1 Phentermine

Kang et al. [42] evaluated the efficacy and safety of phentermine diffuse-controlled release in patients with obesity. Patients were randomized to 12 weeks of treatment with phentermine 30 mg or placebo, administered once daily in patients with obesity with controlled diabetes, hypertension or dyslipidemia. The efficacy was evaluated by changes in body weight and waist circumference (WC) from baseline at 12 weeks and also changes in metabolic parameters, including lipid profiles and blood pressure. The participants in the phentermine group showed significant reductions in body weight (−8.1 ± 3.9 vs −1.7 ± 2.9 kg, p < 0.001) and WC (7.2 ± 0.5 vs 2.1 ± 0.6 cm, p < 0.001) compared with those in the placebo group. Weight reductions of 5% or greater from the baseline (95.8 vs 20.8%, p < 0.001) and 10% or more (62.5 vs 4.7%, p < 0.001) were achieved in the phentermine group and placebo group, respectively. Total cholesterol and LDL-C levels were significantly improved in the phentermine group. However, there were no significant
difference in SBP and DBP between the groups. Dry mouth and insomnia were the most common adverse events, but these were mild to moderate and transient.

Kim et al. [43] conducted a randomized, double-blind, placebo controlled study where 68 relatively healthy obese adults whose BMI was 25 kg/m² or greater received phentermine or placebo controlled study where 68 relatively healthy obese adults these were mild to moderate and transient.

The primary end points were the changes of body weight and WC from baseline in the intention-to-treat population. Mean decrease of both body weight and WC in phentermine-treated subjects were significantly greater than that of placebo group (weight: -6.7 ± 2.5 kg, p < 0.001; WC: -6.2 ± 3.5 cm, p < 0.001). Significant number of subjects in phentermine group accomplished weight reduction of 5% or greater from the baseline and 10% or more (p < 0.001). There were no significant differences in SBP and DBP between the groups (p = 0.122 for SBP; p = 0.219 for DBP).

Weintraub et al. [44] performed a double-blind, controlled clinical trial comparing phentermine resin (30 mg in the morning), fenfluramine hydrochloride (20 mg three times a day) and a combination of phentermine resin (15 mg in the morning) and fenfluramine hydrochloride (30 mg before the evening meal), and placebo. Eighty-one people with simple obesity (130 – 180% of ideal body weight) participated. Individualized diets were prescribed and discussed again during the 24-week study period. Weight loss in those receiving the combination (8.4 ± 1.1 kg) was significantly greater than in those receiving placebo (4.4 ± 0.9 kg) and equivalent to that of those receiving fenfluramine (7.5 ± 1.2 kg) or phentermine (10.0 ± 1.2 kg) alone. Adverse effects were less frequent with the combination regimen than with other active treatments. Thirty-seven participants dropped out of the study, 18 for reasons related to drug treatment. Combining fenfluramine and phentermine capitalized on their pharmacodynamic differences, resulting in equivalent weight loss, fewer adverse effects and better appetite control.

Vallé-Jones et al. [45] carried out a study to compare the effectiveness and tolerance of phentermine and diethylpropion in helping patients more than 20% above their desirable weight to lose weight. Patients were allocated at random to receive either one 30 mg capsule of phentermine or one 75 mg tablet of diethylpropion daily over a period of 12 weeks. They were also asked to restrict their calorie intake to 1500 calories per day. The results showed that there was a significantly greater weight loss in patients treated with phentermine which was particularly marked during the last 4 weeks of the study. There were significant reductions in blood pressure and heart rate in the phentermine group and of heart rate in the diethylpropion group. These were almost certainly related to weight loss rather than to a direct effect of drug treatment. Side effects were generally minor in nature and the incidence and nature of them were comparable in the two groups.

Phentermine proved to be safe also in combination with other forms of weight control therapies like showed by Weintraub et al. [46]. One hundred and twenty one people were enrolled in a 34-week, double-blind clinical trial and randomized to take 60 mg extended-release fenfluramine plus 15 mg phentermine resin versus placebo added to behavioral modification, caloric restriction and exercise. Participants weighed 130 – 180% (154 ± 1.2%) of ideal body weight and were in good health. By week 34, participants receiving active medication lost an average of 14.2 ± 0.9 kg, or 15.9 ± 0.9% of initial weight versus a loss of 4.6 ± 0.8 kg or 4.9 ± 0.9% of initial weight by subjects taking placebo (p < 0.001). On visual analog scales, participants rated fenfluramine plus phentermine as more helpful in reducing hunger than placebo (50.3 ± 0.5 vs 20.3 ± 0.3). Blood pressure decreased and pulse remained unchanged in both groups. Dry mouth was the most common adverse effect in subjects receiving fenfluramine plus phentermine; all adverse effects decreased after 4 weeks. Only nine participants left the study in the first 34 weeks. Two subjects from each group left the study as a result of adverse effects. Overall, fenfluramine plus phentermine used in conjunction with behavior modification, caloric restriction and exercise aided weight loss and continued to be efficacious for 34 weeks.

3.2 Sibutramine

Before the sibutramine withdrawal, our group conducted several studies on sibutramine and its effects on body weight, glycemic control, insulin resistance and inflammation [47-53] in hypertensive obese patients [48], and in obese diabetic patients [47,49-53], in monotherapy [47,49-51] or in association with L-carnitine [52,53]. L-Carnitine is an endogenous molecule involved in fatty acid metabolism, biosynthesized within the human body using amino acids L-lysine and L-methionine, as substrates. L-Carnitine and its esters help reduce oxidative stress, so it has been proposed as a treatment for many conditions including weight loss.

We observed that sibutramine is surely effective in reducing body weight, and WC; furthermore, sibutramine intake has not been associated with any cardiovascular effect and was generally well tolerated. Sibutramine was also effective in improving insulin resistance and inflammatory parameters. In the last study, [52] we enrolled 254 patients with uncontrolled T2DM in therapy with different oral hypoglycemic agents or insulin and randomized them to take sibutramine 10 mg plus L-carnitine 2 g or sibutramine 10 mg in monotherapy. Both sibutramine and sibutramine plus L-carnitine gave an improvement of glycemic and lipid profile, leptin, TNF-α and high-sensitivity C-reactive protein. We also showed that the association sibutramine plus L-carnitine gave a better improvement of body weight, HbA1c, fasting plasma insulin, HOMA-IR (homeostasis model assessment-insulin resistance), vaspin and adiponectin compared with sibutramine alone.

Regarding adverse reactions all the events were reported as mild or moderate; sibutramine intake was not associated with
any cardiovascular effects and was generally well tolerated, even if our studies were not aimed to evaluate the cardiovascular outcome.

This was in line with what reported by Sari et al. [54], they conducted a prospective and randomized study where the study population consisted of 70 obese women with a BMI ≥ 30 kg/m² and normal glucose tolerance. After a diet period of 1 month (baseline), each individual was randomly assigned to receive 15 mg sibutramine or 15 mg sibutramine plus 1700 mg metformin per day for 12 months. Mean weight loss in sibutramine and sibutramine plus metformin groups was 5.3 ± 4.0% (p < 0.001) and 6.8 ± 3.9% (p < 0.001) after 3 months, and 10.5 ± 4.4% (p < 0.001) and 15.7 ± 4.6% (p = 0.007) after 12 months, respectively.

HOMA-IR value also decreased in both sibutramine (p = 0.045 and 0.002) and sibutramine plus metformin group (p = 0.04 and 0.015) after 3 and 12 months, respectively. Similarly, leptin levels decreased in both sibutramine (p = 0.04, 0.01) and sibutramine plus metformin group (p = 0.023, 0.025) after 3 and 12 months, respectively. There was also significant reductions in C-reactive protein levels in both sibutramine (p = 0.045, 0.02) and sibutramine plus metformin groups (p = 0.007, 0.001) after 3 and 12 months, respectively. These decrements of body weight, HOMA-IR, leptin and C-reactive protein levels were not statistically significant between these two groups both after 3 and 12 months (p > 0.05) showing that combination of sibutramine with metformin did not result in any further effects on weight loss, insulin resistance, leptin and C-reactive protein levels when compared with sibutramine alone. Both sibutramine and metformin therapies were well tolerated, and no subject discontinued the therapy because of adverse events. Five patients in combination group and three patients in sibutramine group experienced mild and transient gastrointestinal discomfort.

The withdrawal of sibutramine license has been mainly due to the data reported by SCOUT trial [15], this study is a prospective, randomized, double-blind, placebo-controlled outcome trial conducted in cardiovascular high-risk overweight/obese patients. In this study, 10,744 overweight or obese subjects, 55 years of age or older, 97% with a medical history of cardiovascular disease, 88% hypertension and 84% T2DM were enrolled. All the subjects received sibutramine 10 mg in addition to participating in a weight-management program during a 6-week, single-blind, lead-in period, after which 9804 subjects underwent random assignment in a double-blind fashion to sibutramine 10 mg (4906 subjects) or placebo (4898 subjects). The primary end point was the time from randomization to the first occurrence of a primary outcome event (non-fatal myocardial infarction, non-fatal stroke, resuscitation after cardiac arrest or cardiovascular death) [15]. This study showed that the mean weight loss during the lead-in period was 2.6 kg; after randomization, the subjects in the sibutramine group achieved and maintained further weight reduction (mean, 1.7 kg). The mean blood pressure decreased in both groups, with greater reductions in the placebo group than in the sibutramine group (mean difference, 1.2/1.4 mm Hg). The risk of a primary outcome event was 11.4% in the sibutramine group as compared with 10.0% in the placebo group (p = 0.02). The rates of non-fatal myocardial infarction and non-fatal stroke were 4.1 and 2.6% in the sibutramine group and 3.2 and 1.9% in the placebo group, respectively (p = 0.02 for non-fatal myocardial infarction, p = 0.03 for non-fatal stroke). The rates of cardiovascular death and death from any cause were not increased. In conclusion, this study showed that subjects with pre-existing cardiovascular conditions who were receiving long-term sibutramine treatment had an increased risk of non-fatal myocardial infarction and non-fatal stroke, but not of cardiovascular death or death from any cause.

Analyzing the 6-week lead-in period during which patients received single-blind sibutramine 10 mg/day plus individualized diet and exercise advice, Van Gaal et al. [55] observed that body weight and WC decreased in diabetic patients with a median of 2.1 kg and 2.0 cm (p < 0.001), respectively; body weight decrease of 1.9 kg and WC of 1.5/2.0 cm (men/women) for those on insulin; body weight decrease of 2.3 kg and WC of 2.0 cm (both men and women) in patients without insulin; blood pressure was also reduced (median SBP/DBP -3.5/-1.0 mm Hg) with larger reductions in diabetic patients who were hypertensive (-10.0/-3.0 mm Hg, both p < 0.001) and/or lost the most weight (> 5%). In diabetic patients who entered with blood pressure at target (< 130/85 mm Hg) but did not lose weight (n = 245), increases of +3.5/+2.0 mm Hg (both p < 0.001) were observed. Non-diabetic patients had greater weight loss (2.5 kg), but smaller reduction in BP (SBP/DBP -2.5/-0.5 mm Hg). Pulse rate increases were less in diabetic compared with non-diabetic patients (1.5 vs 2.0 bpm).

These data showed that in high-risk diabetic patients, sibutramine and lifestyle modifications for 6 weeks resulted in small, but clinically relevant, median reductions in body weight, WC and blood pressure, while a small median increase in pulse rate was recorded.

Weeke et al. [56], instead, examined blood lipid changes during this 6-week lead-in period of the SCOUT trial. After 4 weeks, patients experienced mean reductions in LDL-C of -0.19 mmol/l, HDL-C -0.019 mmol/l, very low-density lipoprotein (VLDL-C) -0.08 mmol/l, TC -0.31 mmol/l and Tg -0.24 mmol/l (p < 0.0001 for each). Four-week changes in LDL-C, HDL-C and TC for patients without versus with T2DM were: -0.25 vs -0.18 mmol/l, p = 0.0004 for LDL-C; -0.03 vs. -0.02 mmol/l, p = 0.0014 for HDL-C; -0.37 vs. -0.29 mmol/l, p = 0.0009 for TC. These data showed that short-term weight management with sibutramine therapy in obese or overweight high-risk patients induced significant mean reductions for all lipids. Those without T2DM benefited most; furthermore, patients with hyperlipidemia and the less obese patients also had greater falls in LDL-C and TC during weight loss.
Efficacy and safety of anti-obesity drugs

Caterson et al. [57] evaluated the aspects of the SCOUT trial already examined by Van Gaal et al. [55] plus the incidence of adverse events. There was a low incidence of serious adverse events: in label conformers (conformers): 1.0%; in non-label conformers (non-conformers): 2.8%, and 93% of patients in both groups completed the 6-week period.

3.3 Orlistat

Actually orlistat is the only anti-obesity drug allowed in Europe; it seems to be safe and well tolerated. We conducted several studies on orlistat [48,49,58,61]: at first, we compared orlistat monotherapy with sibutramine [48,49] or placebo [58,59], then we decided to evaluate the effects of a orlistat + L-carnitine combination compared with orlistat alone [60,61]. However, L-carnitine alone showed to have only a little effect on weight loss and appetite suppression [62]. Comparing orlistat with sibutramine, we observed a significant BMI, body weight, WC, hip circumference (HC) and waist/hip ratio (W/H ratio) improvement in both groups but there was a significant SBP and DBP improvement in orlistat group after 12 months (p < 0.05). A reduction of all lipid profile parameters (p < 0.05 for all) was observed in orlistat group, while only a Tg reduction (p < 0.05) was obtained in sibutramine group after 12 months. Of the 109 patients who completed the study, 48.1% of patients in the orlistat group and 17.5% of patients in the sibutramine group had side effects (p < 0.05 vs orlistat group). Side-effect profiles were gastrointestinal events for orlistat and an increase in blood pressure for sibutramine, but it has been controlled by antihypertensive treatment. The vitamin changes were small and all mean vitamin and β-carotene values stayed within reference ranges. No patients required vitamin supplementation [48,49]. Compared with placebo [58,59], instead, orlistat gave a significant reduction of body weight, WC and BMI, not observed with placebo; furthermore, body weight, WC and BMI values registered with orlistat were significantly better than the values observed in the controls after 12 months (p < 0.05). A faster improvement of glycemic profile, and fasting plasma insulin was obtained with orlistat compared with the controls. Furthermore, there was a significant reduction of lipid profile with orlistat, not reached with placebo. Orlistat was also more effective than placebo (p < 0.05) in improving inflammatory parameters, such as adiponectin and TNF-α. Orlistat gave also a decrease of leptin, and high-sensitive C-reactive protein already after 9 months of treatment, while in the control group the decrease was recorded after 12 months of therapy.

Our results were confirmed by Valsamakis et al. [63]; in their study, non-diabetic female subjects were treated with sibutramine 10 or 15 mg/day or with orlistat for weight loss. After 6 months, the sibutramine group had a modest mean weight loss of 5.4% (p < 0.0001), and WC was reduced by 4.5 ± 1.4 cm. There was a decrease in serum resistin, leptin and C-reactive protein levels, and a rise in serum adiponectin (p < 0.05). Change % in BMI was associated with insulin % (p = 0.02, r = 0.53) and leptin % (p = 0.01, r = 0.58). Change in waist was associated with insulin % (p = 0.005, r = 0.75) and resistin % (p = 0.03, r = 20.55). The orlistat-treated group had a mean weight loss of 2.5%. Although this group did not show significant change in metabolic parameters, surprisingly there was a greater decrease of resistin (p = 0.02) associated with comparable % increase in adiponectin and % reduction of WC and C-reactive protein.

This was in line with Kelley et al. [64]; this study was a 1-year multicenter, randomized, double-blind, placebo-controlled trial of orlistat (120 mg three times a day) or placebo combined with a reduced-calorie diet in overweight or obese adults with T2DM treated with insulin alone or combined with oral agents, but with suboptimal metabolic control (HbA1c 7.5 – 12.0%). After 1 year, the orlistat group lost significantly more weight (-3.89 ± 0.3% of baseline body weight) than the placebo group (-1.27 ± 0.3%, p < 0.001). Orlistat treatment, compared with placebo, produced greater decreases in HbA1c (-0.62 ± 0.08 vs -0.27 ± 0.08%, p = 0.002), fasting plasma glucose (-1.63 ± 0.3 vs -1.08 ± 0.3 mmol/l, p = 0.02) and the required doses of insulin and other diabetic medications. Orlistat also produced greater improvements than placebo in TC (p = 0.0002) and LDL-C concentrations (p = 0.001) and LDL/HDL ratio (p = 0.01).

The same conclusion was reached by Jacob et al. [65]; a total of 2550 overweight or obese patients with T2DM were enrolled and randomized to treatment with orlistat 120 mg three times a day (n = 1279) or placebo (n = 1271) for 6 or 12 months. For the whole population, patients treated with orlistat 120 mg had significantly greater mean decreases in fasting plasma glucose compared with placebo-treated patients (-1.39 vs -0.47 mmol/l; p < 0.0001). In addition, orlistat 120 mg provided significantly larger mean decreases in HbA1c compared with placebo (-0.74 vs -0.31%; p < 0.0001). For patients with minimal weight loss (≤ 1% of baseline body weight), orlistat 120 mg still provided a significantly greater decrease in the least square mean value for both fasting plasma glucose (-0.83 vs 0.02 mmol/l; p = 0.0052) and HbA1c (-0.29 vs 0.14%; p = 0.0008) compared with placebo, suggesting that the improvement of glycemic control with orlistat was independent of weight loss.

Hollander et al. [66] conducted a multicenter, 57-week randomized double-blind placebo-controlled study where 391 obese subjects with T2DM, aged > 18 years, with a BMI of 28 – 40 kg/m², clinically stable on oral sulfonylureas, were randomized to take 120 mg orlistat or placebo three times a day with a mildly hypocaloric diet. After 1 year of treatment, the orlistat group lost 6.2 ± 0.45% of initial body weight versus 4.3 ± 0.49% in the placebo group (p < 0.001). Twice as many patients receiving orlistat (49 vs 23%) lost ≥ 5% of initial body weight (p < 0.001). Orlistat treatment plus diet compared with placebo plus diet was associated with significant improvement in glycemic control, as reflected in decreases in HbA1c (p < 0.001) and fasting plasma glucose (p < 0.001) and in dosage reductions of oral
sulfonylurea medication (p < 0.01). Orlistat therapy also resulted in significantly greater improvements than placebo in several lipid parameters, specifically a greater reduction in TC (p < 0.001), LDL-C (p < 0.001), Tg (p < 0.05), apolipoprotein B (p < 0.001) and the LDL-to-HDL-C ratio (p < 0.001). Mild to moderate and transient gastrointestinal events were reported with orlistat therapy, although their association with study withdrawal was low. Fat-soluble vitamin levels generally remained within the reference range, and vitamin supplementation was required in only a few patients.

3.4 Rimonabant

The endocannabinoid system is a complex network that is involved in multiple physiological processes including energy homeostasis [67], drug addiction [68] and the modulation of pain [69]. Several clinical trials [70,71] have demonstrated rimonabant’s efficacy in terms of decreasing body weight and WC, and improving multiple cardiometabolic risk factors [70]. Van Gaal et al. [70], for example, randomized patients with BMI 30 kg/m² or greater, or BMI greater than 27 kg/m² with treated or untreated dyslipidemia, hypertension or both, to receive double-blind treatment with placebo, 5 mg rimonabant or 20 mg rimonabant once daily in addition to a mild hypocaloric diet (600 kcal/day deficit). The weight loss at 1 year was significantly greater in patients treated with rimonabant 5 mg (mean -3.4 kg; p = 0.002 vs placebo) and 20 mg (-6.6 kg; p < 0.001 vs placebo) compared with placebo (-1.8 kg). Significantly more patients treated with rimonabant 20 mg than placebo achieved weight loss of 5% or greater (p < 0.001) and 10% or greater (p < 0.001). Rimonabant 20 mg produced significantly greater improvements than placebo in WC, HDL-C, Tg and insulin resistance, and prevalence of the metabolic syndrome. The effects of rimonabant 5 mg were of less clinical significance. Rimonabant was generally well tolerated with mild and transient side effects.

This was in line with what reported by Pi-Sunyer et al. [71]: 3045 obese or overweight patients were randomized to receive placebo, 5 mg each day of rimonabant, or 20 mg each day of rimonabant for 1 year, and then rimonabant-treated patients were re-randomized to receive placebo or continued to receive the same rimonabant dose, while the placebo group continued to receive placebo during year 2.

Compared with the placebo group, the 20 mg of rimonabant group produced greater mean reductions in weight (-6.3 vs -1.6 kg; p < 0.001), WC (-6.1 vs -2.5 cm; p < 0.001) and level of Tg (percentage change, -5.3 vs 7.9; p < 0.001) and a greater increase in level of HDL-C (percentage change, 12.6 vs 5.4; p < 0.001). Patients who were switched from the 20 mg of rimonabant group to the placebo group during year 2 experienced weight regain, while those who continued to receive 20 mg of rimonabant maintained their weight loss and favorable changes in cardiometabolic risk factors. Rimonabant was generally well tolerated; the most common drug-related adverse event was nausea (11.2% for the 20 mg of rimonabant group vs 5.8% for the placebo group). This study showed that treatment with 20 mg/day of rimonabant plus diet for 2 years promoted modest but sustained reductions in weight and WC and favorable changes in cardiometabolic risk factors.

Després et al. [72] confirmed that compared with placebo, rimonabant at a dose of 20 mg was associated with a significant (p < 0.001) mean weight loss (repeated-measures method, -6.7 ± 0.5 kg, and last-observation-carried forward analyses, -5.4 ± 0.4 kg), reduction in WC (repeated-measures method, -5.8 ± 0.5 cm, and last-observation-carried-forward analyses, -4.7 ± 0.5 cm), increase in HDL-C (repeated-measures method, +10.0 ± 1.6%, and last-observation-carried-forward analyses, +8.1 ± 1.5%) and reduction in Tg (repeated-measures method, -13.0 ± 3.5%, and last-observation-carried-forward analyses, -12.4 ± 3.2%). Rimonabant at a dose of 20 mg also resulted in an increase in plasma adiponectin levels (repeated-measures method, 57.7%, and last-observation-carried-forward analyses, 46.2%; p < 0.001), for a change that was partly independent of weight loss alone.

At the light of these positive effects, Soyka reported that rimonabant presents a substantial risk of depression [13], this was confirmed by Després et al. [72]: this study showed that the most frequent adverse events resulting in discontinuation of rimonabant were depression, anxiety and nausea. For this reason, in October 2008, EMEA suspended rimonabant license across the EU saying that there was an approximative doubling of the risk of psychiatric disorders in obese or overweight patients taking rimonabant compared with those taking placebo [20].

The Study Evaluating Rimonabant Efficacy in Drug-Naive Diabetic Patients (SERENADE) [73] was a 6-month, randomized, double-blind, placebo-controlled trial of 20 mg/day rimonabant in drug-naive patients with type 2 diabetes (HbA1c 7 -10%). Mean HbA1c reduction from baseline was significantly greater with rimonabant versus placebo (-0.8 vs -0.3%, respectively; p = 0.0002). At study end, more patients receiving rimonabant than patients receiving placebo achieved HbA1c < 7.0% (51 vs. 35%, respectively; p = 0.0122). Fasting plasma glucose also improved significantly with rimonabant compared with placebo. Body weight loss from baseline was greater with rimonabant (-6.7 kg) than with placebo (-2.8 kg) at 6 months (p < 0.0001 in group-to-group comparison), with parallel improvements in WC (6 vs. -2 cm; p < 0.0001). HDL cholesterol increased with a treatment difference of +7% (p < 0.0001) and triglycerides improved by -17% (p = 0.0031) in favor of rimonabant. Rimonabant was also associated with significant reductions in non-HDL cholesterol, total cholesterotol-to-HDL cholesterol ratio and apolipoprotein B-to-apolipoprotein A1 ratio.

Total cholesterol and LDL cholesterol did not change, although the mean size of LDL particles increased significantly with rimonabant relative to placebo. Significant improvements occurred with rimonabant versus placebo in levels of adiponectin, HOMA-IR, proinsulin-to-insulin ratio and proinsulin and leptin levels.
4. Future perspective

Some already marketed drugs, approved for other indications, can also be useful for the treatment of obesity. Obesity, in fact, is usually associated with insulin-resistance and T2DM; for the treatment of overweight/obese type 2 diabetic patients currently available drugs are glucagon-like peptide-1 (GLP-1) receptor agonists (exenatide and liraglutide). Both drugs stimulate insulin secretion, inhibit glucagon secretion, increase or sustain the level of GLP-1 in circulation. Notably, they also suppress food intake and appetite. On this basis, several trials conducted in overweight/obese diabetic patients suggest that agonists of GLP-1 receptor have beneficial effects on metabolic regulation and could lead to weight loss, with a mean weight reduction of -3.2 kg in patients without diabetes, and of -2.8 kg in those with diabetes [74-76]. Based on the available data, exenatide and liraglutide should be considered in patients with diabetes who are obese or overweight, even if further studies are needed to elucidate the effects of GLP-1 receptor agonists for the treatment of obese patients without diabetes [70]. Another drug initially assessed for the treatment of early as well as advanced Parkinson’s [77] and Alzheimer’s disease, is tesofensine, a norepinephrine, dopamine and serotonin reuptake inhibitor. At the dosages tested in the initial trials, tesofensine did not meet the predefined efficacy criteria to proceed directly to Phase III trials for these indications. However, a recent meta-analysis showed that tesofensine produced a placebo-subtracted weight loss of 4% for > 14 weeks without any diet and lifestyle therapy, similar to that of sibutramine, but with no effect on blood pressure [78]. For these reasons, tesofensine is now being developed for obesity management.

Regarding other new drugs licensed for obesity, the FDA has not approved a new prescription anti-obesity drug since 1999 when it opened the US market to orlistat. There are at least two new anti-obesity drugs in clinical trials or are awaiting the FDA approval. One is a formulation of low-dose phentermine and topiramate that has been responding to the FDA inquiries into safety as part of its application process and that has recently been shown to be effective for weight loss treatment [79]. A 28-week randomized clinical trial using phentermine with topiramate (92 mg/15 mg and 46 mg/7.5 mg doses) demonstrated a 9.2% weight loss compared with a 6.4% weight loss with topiramate alone, 6.1% for phentermine alone and 1.7% for placebo [80]. The second one is an association of bupropion and naltrexone, bupropion is an atypical antidepressant and smoking cessation aid that activates pro-opiomelanocortin (POMC) neurons and enhances the release of the anorexiant neuropeptide α-MSH (alpha-melanocyte-stimulating hormone) in the hypothalamus, while naltrexone blocks β-endorphin-mediated autoinhibition to sustain α-MSH release [81]. The last one is an association of bupropion and zonisamide, an epilepsy agent. A 12-week randomized clinical trial showed that bupropion combined with zonisamide achieved greater weight loss (7.5%) than zonisamide alone (3.1%) [82].

Moreover, several gut hormone-based treatments for obesity are under investigation in Phase II and III clinical trials, with particular focus on ghrelin, peptide YY, pancreatic polypeptide (PP), amylin, the already discussed GLP-1 and oxyntomodulin. For example, peptide YY helps signals the brain when to stop eating; obese people have low levels of the hormone, so some drug manufacturer are creating manufactured peptide YY versions that patients would inject to integrate the endogenous peptide YY. On the other side, ghrelin is a 28-amino acid peptide synthesized principally in the stomach [83], it acts via the growth hormone secretagogue receptor to stimulate food intake in humans [84]. Antagonists to ghrelin have been used in preclinical studies, paving the way for possible future evaluation as a therapy for obesity in humans [85]. PP, instead, is principally secreted by a population of cells located at the periphery of pancreatic islets; it is released into the circulation in a biphasic manner in response to nutrient ingestion and is subject to control by the vagus nerve and a number of other factors [86]. PP reduces food intake when administered to humans [87], for this reason a PP analog has been developed to improve the suppressor effect on appetite. Amylin, instead is co-secreted with insulin from the β-cells of the pancreas. Pramlintide is an amylin analog that has recently been granted the FDA approval. In addition to favorable effects on blood glucose, pramlintide reduces food intake and has been shown to result in 1.8 kg reduction in body weight over 26 weeks in overweight diabetic subjects [88]. Further evaluation of this drug as a therapy specifically for the treatment of obesity is awaited. Oxyntomodulin is co-secreted with GLP-1 and peptide YY into the circulation by intestinal L-cells after nutrient ingestion, and it is a satiety signal, its administration reduces energy intake in humans [89].

5. Conclusions

All data considered, we can conclude that, even if orlistat is not as effective as the other drugs in reducing body weight, at the moment it is the only available choice for the treatment of obesity, because of its safety on cardiovascular events and its positive effects on diabetic control.

6. Expert opinion

We already know that major direct complications of obesity are insulin resistance and T2DM [90], it is also know that early weight loss during a weight loss program is generally considered to predict long-term weight outcome in obese patients [91], and this is reflected in prescribing guidelines for anti-obesity drugs. Furthermore, it emerged that modest weight loss may reduce or even eliminate the need for hypoglycemic agents and may lessen the severity of cardiovascular disease risk factors, which are typically altered in patients with T2DM [92]. Regarding orlistat, data collected showed that orlistat is an effective treatment modality in overweight...
or obese patients with T2DM even in those who have suboptimal metabolic control with insulin therapy; orlistat gave a clinically meaningful weight loss and maintenance of weight loss, improved glycemic control and improved lipid profile, also reducing cardiovascular disease risk factors. Moreover, even a modest weight loss (>5%) after medical treatment with orlistat in a routine obesity hospital clinic has been associated with improvements in insulin sensitivity and with potentially favorably changes in serum adipocytokines, particularly in a rise of serum adiponectin. Furthermore, orlistat proved to be a safe drug except for some minor gastrointestinal adverse effects; for these reasons, we think that orlistat should be the first choice for the treatment of obesity.

Regarding sibutramine, this drug is not available anymore, even if some concerning about the results showed by the SCOUT trials are due to the population selected for the study. According to the previously approved EU label (Summary of Medicinal Product Characteristics), in fact, sibutramine was contraindicated in patients with a history of coronary artery disease, congestive heart failure, tachycardia, peripheral arterial occlusive disease, arrhythmia or cerebrovascular disease[93]. In the SCOUT trial, instead, the population enrolled included both overweight/obese patients with increased risk of cardiovascular disease due to obesity-related risk factors such as T2DM and those with a history of cardiovascular disease such as myocardial infarction or stroke in whom sibutramine should not be administered. For those reasons, we think that an increase of cardiovascular diseases in non-conformers patients has to be expected and this should not have to influence the use of sibutramine in conformers patients.

Regarding rimonabant we do not think that it could be a safe drug, because of the reported increased numbers of psychiatric diseases even in patients who never had suffered from these diseases before [13]. On the other side, phentermine has a better effect on body weight compared with all the other drugs, a short-term phentermine treatment resulted in significant reduction in weight and improvement of metabolic parameters, including WC and some lipid profiles, without clinically severe adverse events. The problem with phentermine is that the treatment of obesity required a long-term therapy, if not at the suspension of the drugs the patients regain weight, and phentermine can be taken only for a short period of time.

**Declaration of interest**

The authors certify that they have no affiliation with, or financial involvement in, any organization or entity with a direct financial interest in the subject matter or materials discussed in the manuscript.

**Bibliography**

Papers of special note have been highlighted as either of interest (●) or of considerable interest (●●) to readers.


11. WIN-Publication-Prescription Medications for the Treatment of Obesity. National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), National Institutes of Health; Bethesda; 2009


Efficacy and safety of anti-obesity drugs


This study showed the efficacy of orlistat in combination with l-carnitine in reducing body weight and inflammatory parameters in type 2 diabetic patients.


71. Pi-Sunyer FX, Aronne LJ, Heshmati HM, et al. 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 2006;295:761-75


** This meta-analysis evaluates the anti-obesity effect of exenatide and liraglutide both in diabetic and non-diabetic patients.


78. Larsen MH, Rosenbrock H, Sams-Dodd F, Mikkelsen JD. Expression of brain derived neurotrophic factor, activity-regulated cytoskeleton protein mRNA, and enhancement of adult hippocampal neurogenesis in rats after sub-chronic and chronic treatment with the triple monoamine re-uptake inhibitor
tesofensine. Eur J Pharmacol 2007;555:115-21


81. Vivus, Inc. VIVUS Announces Positive Results From Two Phase 3 Studies: Obese Patients on Qnexa Achieve Average Weight Loss up to 14.7% and Significant Improvements in Co-Morbidities: Results of EQUIP and CONQUER Phase 3 Studies Exceed FDA Benchmarks for Obesity Treatments, Demonstrate Positive Safety Profile. Available from: http://ir.vivus.com/releasedetail.cfm?ReleaseID=407933


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