

Pharmacotherapy of obesity

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Obesity is a major health problem with significant comorbidities. Its prevalence has dramatically increased over the last few decades, so that it is considered an international epidemic. Large epidemiologic studies have clearly associated obesity with cardiovascular disease and side effects in almost every organ system, so that the need for treatment appears to be imperative. Several short- and, recently, long-term anti-obesity drugs have been evaluated, but so far there is no 'magic pill' that could permanently cure or control obesity, although a number produce significant health benefits from a medical point of view. Orlistat, sibutramine and rimonabant are the most widely used anti-obesity drugs in clinical practice, while new, much more promising ones will be in the market in the following few years.

Obesity, a sign of power and wealth in the past, is today the most common nutritional disorder and major health problem with significant comorbidities. Its prevalence has dramatically increased over the last several decades throughout the world, so that it is no exaggeration to state that it is an international epidemic. It has been estimated that approximately 315 million people worldwide meet the WHO criteria of obesity.

The WHO has defined obesity as a 'disorder of body composition in that there is an abnormal, absolute or relative proportion of body fat in relation to lean body mass, to the extent that health is impaired.' An increase in sedentary lifestyle seems to be one of the principal reasons for the dramatic increase in obesity's prevalence. The so-called 'comfort eating', rich in saturated fats and sugars, causes an increase in average energy intake per person, which in combination with decreased physical activity, contributes to weight gain. An individual's genetic background is also believed to predispose to obesity, through the metabolic and endocrine disturbances it induces. However, as the obesity epidemic has occurred too rapidly to be accounted for by changes in the genetic pool alone, it is clear that environmental factors, in particular the fat- and sugar-rich diets and the reduction in physical activity, are the key to the current epidemic.

Being widely spread in all age groups and associated with several potentially life-threatening cardiovascular and metabolic disorders as well as impaired quality of life, obesity is a chronic disease that demands treatment.

Overweight & obesity classification: risk status assessment

Large epidemiologic studies recognize obesity as a major risk factor for cardiovascular disease (CVD), while at the same time it is considered causally related to increased long-term comorbidity and mortality from all causes. Hypertension, hyperlipidemia, obstructive sleep apnea and Type 2 diabetes are only some of the obesity-related diseases, while some types of cancer, such as breast, colon, prostate and endometrial cancer, are also more common in obese individuals. According to the National Health and Nutrition Examination Survey (NHANES) III, the morbidity and mortality rates are closely related to the degree of obesity, making the classification of the weight status imperative, as this enables health practitioners to stratify individuals' health risk and, thus, modify the level of intervention accordingly. BMI and waist circumference are used in clinical practice for the estimation of weight status, while the presence of obesity-related disorders, such as hypertension and dyslipidemia, further increase the overall mortality risk [101].

BMI is derived by dividing the body weight (kg) by the square of the height (m). It is considered a relatively accurate marker of total body fat mass. Generally, individuals with a BMI between 18.5 and 24.9 kg/m² are classified as normal weight, while those with a BMI of 25–29.9 kg/m² are considered overweight. Patients with a BMI of 30–34.9 kg/m² are classified as obese Class I, those with a BMI of 35–39.9 kg/m² are classified as obese Class II and, finally, those with a BMI of 40 kg/m² or

Keywords: anti-obesity drugs, BMI, obesity, obesity classification, orlistat, rimonabant, sibutramine

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over are classified as extremely obese Class III. NHANES III suggests gradual increase in morbidity and mortality rates at BMI values greater than 25 kg/m². The results of the Lewin study [101] are also compatible with the NHANES III findings, suggesting a direct correlation between increased BMI and prevalence of comorbid conditions, especially Type 2 diabetes, hypertension, heart disease, stroke and arthritis (Table 1).

The waist circumference is used in clinical practice for the evaluation of central obesity. Of course, waist circumference measures all adipose tissue (and everything else) localized at the centre of the body and specific ethnic and age-related modifications may be necessary when interpreting its values; however, it is generally considered an easy, accurate and useful measurement to describe visceral adipose tissue accumulation in clinical practice. This is considered an independent risk factor for the development of cardiovascular and metabolic disorders [1,2] and, thus, the distinction between visceral and peripheral fat is very important. Most studies suggest that the incidence of obesity-related diseases is higher at waist circumference values greater than 94 cm in men and 80 cm in women, while more sophisticated cardiovascular risk charts, such as those from the Framingham study, help to identify individuals at increased cardiovascular risk whose BMI is not yet significantly abnormal, but whose waist circumference is.

Clinical management

It is now well determined that even a small amount of steady weight loss, of approximately 5–10% of the initial body weight, ensues significant health benefits, as it improves metabolic and cardiovascular risk factors and prevents the progression to Type 2 diabetes. The results of several studies, such as the Chinese, the Finnish and the US Diabetes Prevention Program, are compatible with this estimation. By contrast, if

weight is regained, health risks increase again, suggesting obesity is a chronic disease that needs long-term or even lifelong treatment.

As the successful management of obesity requires constant effort from the patient's side, their readiness and motivation to lose weight should be assessed before deciding the weight-loss strategy. It is very important to assess the support from friends and family and the potential barriers to this strategy. Achievable goals should be set, while in order to elicit their maximum effort for the requested lifestyle changes, individuals' preferences, likes and dislikes should be taken into account before the selection of a tailored weight-loss program.

According to NICE guidelines, people with a BMI of less than 25 kg/m² are not candidates for weight management but rather for prevention of weight gain, while those with a BMI of 30 kg/m² or over need treatment. Individuals with a BMI between 25 and 29.9 kg/m² should be treated only if they also have obesity-related comorbidities or high waist circumference, since both increase the overall mortality risk. Weight loss of 10% of the initial body weight achieved over 6 months with a rate of weight loss of 0.5–1 kg per week is generally the recommended target, as greater rates of weight loss do not achieve better long-term results. The combination of diet, exercise and behavior therapy remains the gold standard of the weight-loss programs, and only if they fail should pharmacotherapy or even surgery be considered (Table 2).

Diets of 1000–1200 kcal/day for women and 1200–1600 kcal/day for men, which means a reduction of 500–1000 kcal in caloric intake per day from the current level, are usually recommended for weight loss. Regular meals and plenty of fiber-rich foods, fruits and vegetables, in place of foods high in fat and sugar, are strongly recommended by NICE [3]. Patients' education regarding caloric counting, food preparation, composition

Table 1. Increased risk of obesity-related diseases with higher BMI.

Disease	BMI of 25 or less	BMI 25–30	BMI 30–35	BMI of 35 or more
Arthritis	1.00	1.56	1.87	2.39
Heart disease	1.00	1.39	1.86	1.67
Diabetes (Type 2)	1.00	2.42	3.35	6.16
Gallstones	1.00	1.97	3.30	5.48
Hypertension	1.00	1.92	2.82	3.77
Stroke	1.00	1.53	1.59	1.75

Adapted from the American Obesity Association Centers for Disease Control Third National Health and Nutrition Examination Survey. Analysis by The Lewin Group, 1999 [101].

Table 2. The level of intervention to discuss with the patient.

Body weight – BMI (kg/m ²) classification	Waist circumference			Comorbidities present
	Low	High*	Very high*	
Overweight (25.0–29.9 kg/m ²)	General advice on healthy weight and lifestyle	Diet and physical activity	Diet and physical activity	Diet and physical activity; consider drugs
Obesity Class I (30.0–34.9 kg/m ²)	Diet and physical activity	Diet and physical activity	Diet and physical activity	Diet and physical activity; consider drugs
Obesity Class II (35.0–39.9 kg/m ²)	Diet and physical activity; consider drugs	Diet and physical activity; consider drugs	Diet and physical activity; consider drugs	Diet and physical activity; consider drugs; consider surgery
Obesity Class III (≥40 kg/m ²)	Diet and physical activity; consider drugs; consider surgery	Diet and physical activity; consider drugs; consider surgery	Diet and physical activity; consider drugs; consider surgery	Diet and physical activity; consider drugs; consider surgery

*For men, waist circumference of less than 94 cm is low, 94–102 cm is high and more than 102 cm is very high. For women, waist circumference of less than 80 cm is low, 80–88 cm is high and more than 88 cm is very high.

Data taken from the NICE guidelines for obesity 12/2006 [3].

and portion size make the success of the required long-term changes more likely, and should always be an integral component of the dietary therapy.

Physical activity contributes to weight loss by increasing the total energy expenditure, but also maintains muscle mass, which decreases with weight loss. It also increases the level of endorphins in the body and thus reduces psychological stress, which is usually increased in obese individuals during dieting periods, but most importantly reduces the severity of obesity-associated cardiovascular risk factors. Physical activity should be gradually increased in obese patients, so that accidents are avoided. Approximately 30–45 min of moderate physical activity as part of everyday life is considered of great benefit, while the minimization of sedentary activities is the best start in this direction.

Obese individuals who participate in weight-loss programs are asked to change lifelong habits in a very short period of time, and that fact inevitably restricts the likelihood of successful outcome of their attempt. Tailored methods and behavior-change strategies that help the obese patients to overcome potential barriers in their compliance with dietary and physical activity instructions and which help them improve their food quality, increase their physical activity level and reduce their energy intake are important components of weight loss strategies and are part of the so-called behavior therapy [3,101].

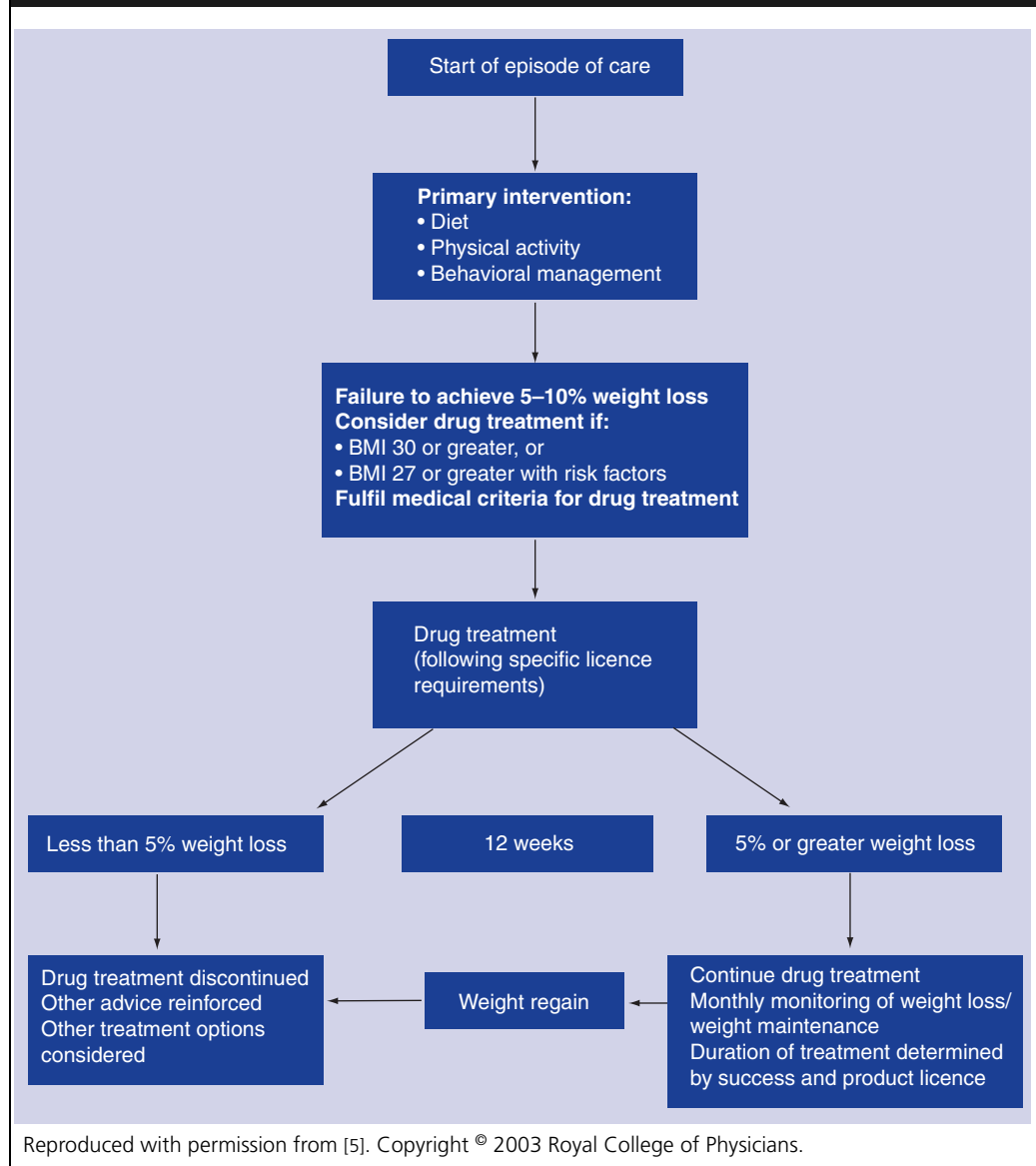
If diet, exercise and behavior therapy fail to achieve the desired weight loss, only then should pharmacotherapy or even surgery be considered (Figure 1).

Pharmacotherapy of obesity

Although the principle of treating obesity is simple, production of negative energy balance, the reality is very different. Owing to a powerful internal biological system based on survival that tends to maintain and restore the fuel stores and return body weight to the baseline value, any weight loss triggers a series of neuroendocrine effects that resist any further weight loss, leading to failure of most of the obesity treatments relying on lifestyle changes alone. This is exactly the crucial moment that a pharmacologic intervention can overcome any internal biopsychologic barriers, leading weight-loss attempts to a successful outcome.

The use of drugs in weight management has been an area of great interest for many years. Until recently, the recommended drugs were licensed for short-term use only, owing to their potential for abuse or development of serious side effects. Fenfluramine and its isomer dexfenfluramine are the most recent anti-obesity medications to be withdrawn from the market as they were causatively related to primary pulmonary hypertension and valvular heart disease development. The recent change in the view of obesity and its recognition as a serious chronic relapsing disease that requires long-term or even lifelong treatment led researchers to the investigation of anti-obesity drugs that could meet the novel requirements. Generally, the ideal anti-obesity drug should combine effectiveness and safety. Although such a drug has not yet been developed, some progress in this direction has already been made, as the newer drugs are generally safer and appropriate for longer use in comparison with the oldest drugs.

Figure 1. Management pathway for the appropriate prescription of an anti-obesity drug.



The current accepted pharmacotherapy treatments include two main classes of weight-loss drugs:

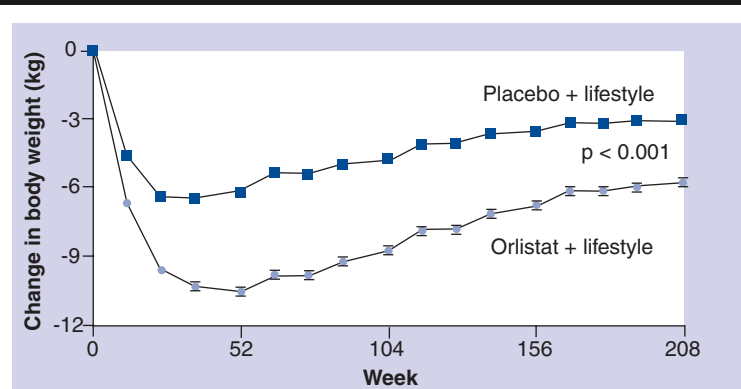
- Those that suppress the appetite and increase satiety, the so-called appetite suppressants;
- Those that act in the gastrointestinal tract and decrease the food-energy absorption (orlistat).

Most of the appetite suppressants exert their effect by affecting the monoamine and neuropeptide pathways of the CNS (e.g., sibutramine and phentermine), while rimonabant is the only one in market that blocks the endocannabinoid system. The combined use of anti-obesity drugs

is not yet approved, as more side effects and no benefits for weight-loss management have been reported [3].

According to NICE guidelines, pharmacotherapy is indicated in patients with a BMI of 30 kg/m² or over, as well in those with a BMI of 27 kg/m² or over if established obesity-related comorbidity (CVD, Type 2 diabetes mellitus or sleep apnea) or three or more cardiovascular risk factors (such as smoking, hypertension, dyslipidemia and so on) are present. In any case, pharmacotherapy should only be recommended as adjunct to lifestyle modifications if they have failed to achieve the desired weight loss on their own.

Figure 2. Weight loss (mean \pm SEM) during 4 years of treatment with orlistat plus lifestyle changes or placebo plus lifestyle changes in obese patients (LOCF data).



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The potential benefits and limitations of these medications, as well as their side effects and the potential impact on the life of the candidate user, should be thoroughly explained and information on services that provide advice or support on patients should be also provided, if available. Patients who are receiving pharmacotherapy should be frequently assessed by the health professional for the success, the necessity of continuation and the safety of the pharmacological intervention. The decision in favor of one drug depends generally upon individual considerations, including portion sizes, snacking behavior and dietary fat content, as well as the presence of specific contraindications. If, at any time, it appears that the program is failing, a reassessment to determine the reasons should take place before discontinuance of the treatment is decided [101].

Orlistat

Orlistat (tetrahydrolipostatin) is a drug that promotes weight loss by preventing the digestion and absorption of dietary fat from the gut. In the intestine, there are enzymes known as lipases that break up the dietary triglycerides into the smaller glycerol and fatty acid molecules so that they can be absorbed into the body. Orlistat inhibits lipases by binding to their active serine residue in the gut. The unabsorbed part of the fat is later excreted in the feces. As the drug leaves the stomach rapidly, only lipases released soon after the meal is consumed are inhibited, whereas fats are released by the stomach over several hours. The degree of the ingested fat malabsorption is curvilinearly related to the dose of the administered orlistat, and the maximum plateau value of its malabsorption-fecal excretion occurs at a dose of 360 mg of orlistat per

day. At this dose, it is estimated that approximately 30% of the alimentary fat is excreted intact. As the typical western diet derives approximately 40% of its calories from fat, orlistat may be a useful adjunct in weight-loss strategies, especially in individuals with fat-rich dietary habits [4,5].

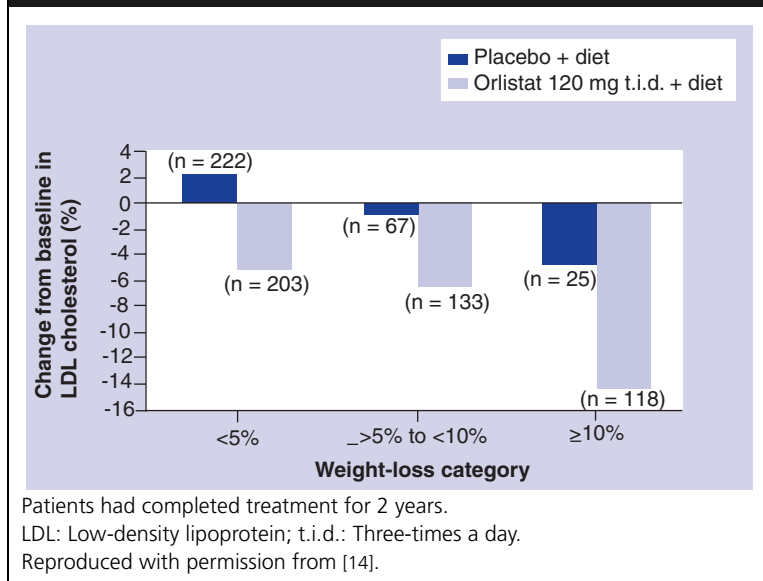
Orlistat was approved by the US FDA in April 1999 for long-term use (up to 2 years). Many clinical trials that have thoroughly researched its safety and efficacy over months and years, as well as its effectiveness in weight-management programs, demonstrated that the weight loss achieved by the combination of 120 mg of orlistat three-times daily with hypocaloric diets is significantly more than that achieved by hypocaloric diets alone. They also constantly demonstrated that an individual is more likely to maintain any weight loss while on orlistat than on weight-maintenance diets only (Figure 2).

In addition, it was estimated that owing to its method of action, orlistat reduces low-density-lipoprotein (LDL) cholesterol beyond what could be expected from weight loss alone [6], whilst also having a beneficial effect on blood pressure and HbA_{1c}. Supporting these promising results are those of the prospective, double-blind, randomized, placebo-controlled, 4-year XENical in the prevention of Diabetes in Obese Subjects (XEN-DOS) study [7], which demonstrated that orlistat, further to significantly increasing weight loss, also reduces the incidence of diabetes by 37% more than the conventional lifestyle interventions alone. The relative reduction is even higher in the impaired glucose tolerance patients (-45%) in comparison with the placebo-treated ones. It also confirmed the favorable effects of orlistat on several cardiovascular risk factors, such as blood pressure, lipids, waist circumference, fibrinogen and plasminogen activator inhibitor-1, providing further support to the multiple metabolic benefits that its administration in overweight and obese individuals may cause (Figure 3) [8].

Orlistat is basically considered to be more effective in the management of those who [5]:

- Have lost at least 2.5 kg in weight prior to consideration of drug treatment;
- Require longer-term behavioral change;
- Follow a high-fat diet;
- Have elevated LDL cholesterol values;
- Have impaired glucose tolerance or diabetes;
- Have repeatedly lost weight in the short-term and then rapidly regained it;
- Have the ability to adhere to a low fat diet for the longer term.

Figure 3. Mean percentage change from baseline low-density lipoprotein cholesterol levels in orlistat- versus placebo-treated patients in an at-risk population with baseline levels over 130 mg/dl.



The continuance of its therapy beyond 3 months is only recommended for individuals who have lost at least 5% of their initial body weight since starting the treatment. However, as the rates of weight loss may be slower in people with Type 2 diabetes, achievable goals and less strict targets should be set in this group of patients. At the moment, its combined usage with other weight-loss medications is not approved by NICE and treatment with orlistat for longer than 12 months is a decision that should be made, through negotiation between the health professional and the patient, based on the potential benefits and limitations of such a decision. It is estimated that prescriptions for orlistat have increased by 36-fold in recent years [9].

Gastrointestinal events, such as oily leakage from rectum, flatulence, fecal urgency, liquid or oily stools, fecal incontinence, abdominal distension and pain, which are related to the mode of action of orlistat, occur mainly in patients who do not comply with a low-fat diet. However, they are generally mild to moderately severe, and their frequency usually decreases after a few weeks of treatment. Administration of psyllium mucilloid once-daily has been shown to decrease the frequency and severity of adverse effects [10]. Owing to its safety, orlistat can be used in patients requiring longer-term treatment. Systemic absorption of orlistat is very low (<1%) and thus its systemic side effects, such as oxalate-induced renal stones

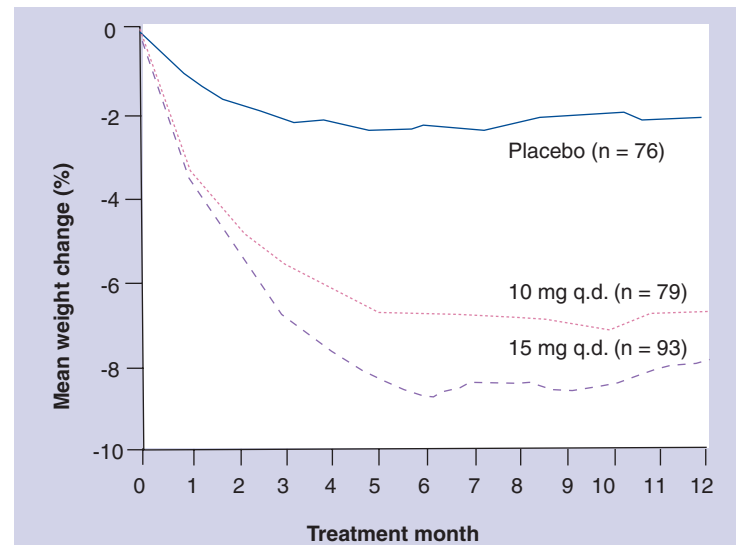
and vitamin deficiency, stem from its malabsorptive effects. Deficiency of the lipophilic vitamins A, D, E and K may follow long-term treatment with orlistat, making the usage of multivitamin supplements necessary when orlistat is used for a long time. Attention to potential interactions is also needed. The manufacturer of orlistat advises avoidance of its concomitant use with acarbose, owing to increased incidence of gastrointestinal side effects, as well as its concomitant use with amiodarone and cyclosporin, as orlistat might reduce their absorption. By affecting vitamin K absorption from the gut, orlistat may potentiate the anticoagulant effect of coumarins, and close monitoring of international normalized ratio is necessary in such cases [102].

Sibutramine

The importance of the CNS monoamine and neuropeptide pathways in food-intake regulation has been intensively studied in recent years. The documentation that as well as moderating mood and various other processes in the brain, the stimulation of the serotonin and the noradrenergic receptors in the paraventricular nucleus (PVN) of the hypothalamus modulates feeding and affects the meal quality and size by blocking the hunger signal and enhancing the feeling of fulfilment from eating paved the way for the development of appetite suppressants. Some drugs of this category affect catecholamines (e.g., dopamine and norepinephrine), and others affect monoamines (e.g., serotonin), while others affect more than one neurotransmitter. Sibutramine was approved by the FDA in November 1997 for body weight management. It is a centrally acting appetite suppressant that inhibits the reuptake of norepinephrine (by 54%), serotonin (by 53%) and, to a lesser extent, dopamine (by 16%). It belongs to the so-called adrenergic and serotonergic weight loss agents and is the only drug of this class approved for long-term use (up to 12 months). In addition to its appetite-suppressant effects, sibutramine also increases thermogenesis and thus the total energy expenditure, which is considered another mechanism by which it contributes to weight loss.

Many prospective, randomized, controlled clinical trials have estimated sibutramine's safety and efficacy in weight management and assessed its effectiveness according to the given dose. Meta-analysis of 29 trials [11] clearly supports the role of sibutramine in weight-loss strategies, while at the same time it emphasizes again the importance of its combination with lifestyle modifications. Another 1-year study that compared the effectiveness of 10

Figure 4. Mean weight change (%) in sibutramine 10 mg versus sibutramine 15 mg versus placebo-treated patients over 12 months.



q.d.: Once daily.

Reproduced with permission from [14].

and 15 mg of sibutramine versus placebo in patients who were already following a hypocaloric diet, suggested that in comparison with the placebo-treated group, in which the weight loss was approximately 2% of the initial body weight, the weight loss of the 10 mg- and 15 mg-treated groups was 6.5 and 8%, respectively (Figure 4) [1,12].

Although the effectiveness of sibutramine as a weight-loss drug was supported by multiple clinical trials, most of them demonstrated weight regain after discontinuation of therapy. The Sibutramine Trial of Obesity Reduction and Maintenance (STORM) study focused exactly on the assessment of the long-term (2 years) effectiveness of sibutramine in weight-loss maintenance. At the end of the study, it was estimated that it reduces weight regain even after many months (18 months) of discontinuation, while at the same time, multiple benefits in the metabolic profile of the sibutramine-treated group were also maintained (reduction of triglycerides, very low-density lipoprotein [VLDL], insulin resistance and increase of the high-density-lipoprotein [HDL] blood levels), supporting its potential role as a metabolic risk-factor modulator, especially in obese individuals with low HDL values. Finally, an ongoing multicenter, double-blind, placebo-controlled trial, the Sibutramine Cardiovascular Outcome Trial (SCOUT) study, which started in 2003 and will continue until

2008, is designed to assess the effect of sibutramine on the morbidity and mortality values of overweight and obese patients with high risk of CVD. The results of this study are expected to illustrate the potential benefits of sibutramine treatment on cardiovascular outcomes [13].

Although it is not always possible to predict precisely which patients are going to respond to this drug therapy and how much weight they may lose, more often, initial responders continue to respond, whereas initial nonresponders do not usually respond, even with an increase in dosage [6]. Like other anti-obesity drugs, sibutramine is indicated as adjunct to lifestyle changes in patients with a BMI of 30 kg/m² or over, a BMI of 27 kg/m² or over and established obesity-related comorbidity, or a BMI of 27 kg/m² or over and three or more cardiovascular risk factors present, especially in [5]:

- Those whose appetites and eating habits are uncontrollable
- Frequent snackers
- Nocturnal eaters
- Those who need immediate weight loss for medical reasons
- Patients with low HDL cholesterol values
- Those with no contraindications to its use

Generally, sibutramine starts working quickly, with most of its users losing weight within the first 8 weeks of treatment, and most of the weight loss occurring within the first 6 months of therapy [14]. The suggested starting dose is 10 mg in the morning, which is increased to 15 mg daily if weight loss is less than 2 kg, following 4 weeks of treatment with 10 mg daily. The 5-mg dosage is only recommended for those who are intolerant to the 10-mg dose. As a 3-month period is considered sufficient to identify the responders to sibutramine therapy, NICE recommends discontinuation of the treatment if less than 5% of the pretreatment body weight has been lost 3 months after the initiation of the treatment. The exception to this rule are the Type 2 diabetics, who generally have more difficulty losing weight, and for whom lower targets should be set.

Sibutramine is generally well absorbed from the gastrointestinal tract (77%). Although it is metabolized considerably in its first pass by the cytochrome P450 isoenzyme CYP3A4 and has a half-life of only 1 h, both of its metabolites (amines, called active metabolites 1 and 2) are active, with half-lives of 14 and 16 h, respectively, prolonging its action. The most common side effects that

have been reported by users of sibutramine in many clinical trials were an increase in blood pressure and, in some cases, in heart rate. The British National Formulary recommends that the blood pressure and heart rate should be monitored every 2 weeks for the first 3 months, then monthly for 3 months, and then at least every 3 months thereafter. The medication should be stopped if blood pressure exceeds 145/90 mmHg or if systolic or diastolic pressure is raised by 10 mmHg or more or if pulse rate is raised by 10 bpm or more at two consecutive visits. The drug is generally contraindicated in patients with history of coronary artery disease, congestive heart failure, arrhythmias and stroke disease, as well as in those with hyperthyroidism and pheochromocytoma and in those who are receiving treatment with monoamine oxidase inhibitors or selective serotonin-reuptake inhibitors (SSRIs). Prostatic hypertrophy, pregnancy and lactation are also strong contraindications to sibutramine usage [102]. It is estimated that prescriptions for sibutramine have increased by fourfold in recent years.

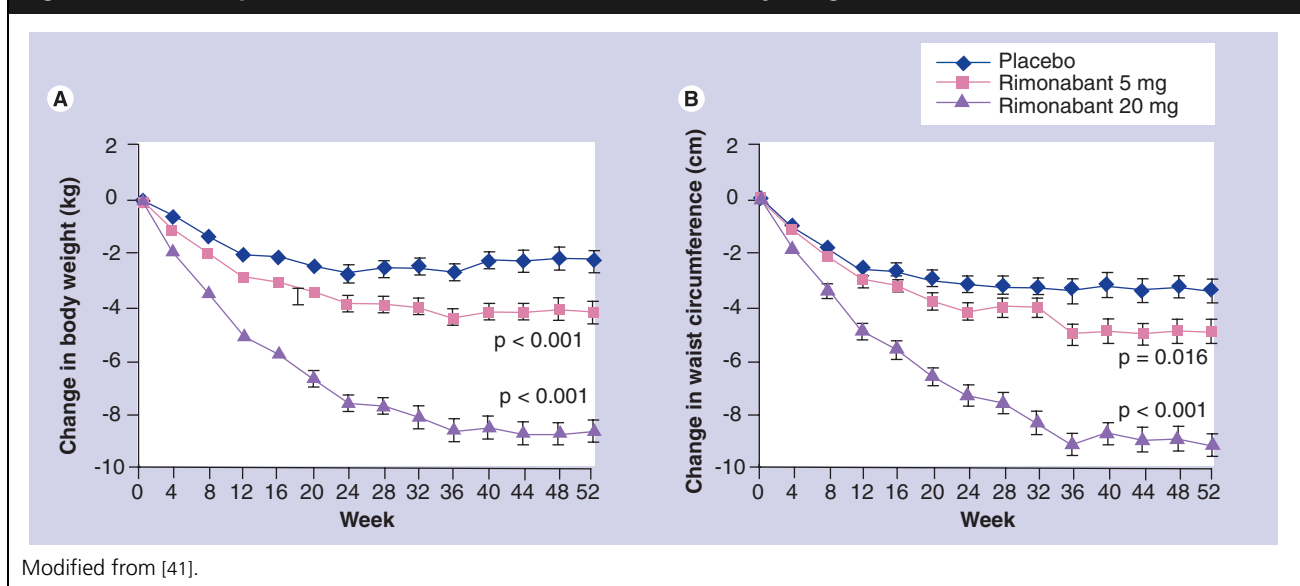
Rimonabant

The observation that cannabis smokers often experience extreme hunger pangs led scientists to the discovery and characterization of the endocannabinoid system. The presence of its receptors has been documented in many areas of the brain, such as those involved in pleasure, memory, thought, concentration and so on [7]. However, the identification of the CB1 cannabinoid receptors in the hypothalamus and the documentation

that their stimulation increases appetite raised the challenge for the development of CB1 blockers that could lead to appetite suppression and weight loss. In 1994, researchers produced the first CB1-receptor-specific antagonist, rimonabant, which when administered in animals, reduced their appetite and food intake and caused weight loss. Since then, rimonabant has been approved for clinical use in obese people.

Data from several studies support that the endocannabinoid system is overactivated in obese individuals, implying a causative role in the development of obesity. In addition, receptors of this system have been identified in organs with a regulatory effect on metabolism, such as the adipose tissue, liver, skeletal muscle, pancreas and gut, which could mean involvement of the endocannabinoid system in the pathogenesis of the adverse metabolic changes presented in obesity (metabolic syndrome). The Rimonabant In Obesity (RIO) study is a multicenter, international, prospective, randomized, placebo-controlled study, consisting of four Phase III trials, the RIO-Diabetes, RIO-Lipids, RIO-North America and RIO-Europe, designed to estimate the effect of rimonabant on several metabolic risk factors, as well as its safety and efficacy as a weight-loss drug, in different target groups. The data analysis of this study suggests that, in comparison with the placebo treatment, daily administration of 20 mg rimonabant results in significant weight loss (Figure 5) and improvement in a cluster of cardiovascular risk factors of metabolic origin that comprise the metabolic

Figure 5. Effect of placebo or rimonabant for 52 weeks on body weight and waist circumference.



Modified from [41].

syndrome (e.g., triglycerides, HDL, insulin sensitivity, C-reactive protein, blood pressure, waist circumference), as well as a shift of the LDL small dense molecules towards less atherogenic ones [15–18].

Surprisingly, it was estimated that the improvements in insulin resistance, HbA_{1c}, HDL and triglycerides were beyond that expected by weight loss alone, implying weight-independent effects on the metabolic profile (Table 3) [15,18,19]. It has been suggested that the separate weight-dependent and -independent metabolic effects of rimonabant may be explained by the physiology of the endocannabinoid system and the expression of the CB1 receptors in peripheral tissues, while the direct boosting effect of rimonabant on adiponectin production, which increases by 57% more than could be expected from weight loss alone in rimonabant-treated individuals, provides an additional metabolic pathway that could contribute to the beyond weight loss metabolic effects of rimonabant, by which it eventually reduces the incidence of CVD and Type 2 diabetes. The beneficial cardiovascular and metabolic modulating role of rimonabant has been well established in overweight and obese individuals with or without Type 2 diabetes and/or dyslipidemia [15]. More importantly, according to RIO-North America and RIO-Europe trials [16,20,21], the achieved metabolic and body weight benefits are maintained for at least 1 year after discontinuance of rimonabant.

Rimonabant may be more useful in Type 2 diabetics, who need adjunct therapy with appetite suppressants and who are unable to take or tolerate sibutramine. Rimonabant is licensed for up to 2 years use, while caution is needed when used by patients with epilepsy, mild-to-moderate hepatic impairment, uncontrolled psychiatric illness and those aged over 75 years. It is strongly contraindicated during pregnancy, breastfeeding

and severe renal or hepatic impairment, while nausea, vomiting, diarrhea, dry mouth, mood changes, anxiety, irritability, nervousness and sleep disorders seem to be its most common side effects. However, the main area of concern is the potential for serious depression and suicidal ideation, although it is uncommon. This needs to be carefully monitored and the drug stopped early if signs of depression develop (Table 4).

Other potential weight-loss drugs

Investigational compounds for the treatment of obesity act via appetite regulation, appetite regulation plus metabolic properties, increased energy expenditure/fat oxidation or decreased food absorption. Appetite regulation involves many potential pathways; however, the most promising drug-development approaches target pure CNS pathways or peripheral signals to the CNS. Recently, the potential use of the gut hormones GLP-1 and cholecystokinin (CCK) in weight-loss strategies, as agents that affect peripheral signals to the CNS, has been intensively investigated.

Incretins (GIP and GLP-1) are hormones with glucoregulatory effects, produced by the endocrine cells of the intestine following ingestion of food. Exenatide is an incretin mimetic with properties similar to human GLP-1 that was recently approved for the treatment of Type 2 diabetes (marketed as Byetta®), as it enhances glucose-dependent insulin secretion. However, it may also emerge as an off-label obesity-treatment drug, as it attains appetite-suppressant effects. Clinical trials have demonstrated that most people using exenatide slowly lose weight and generally the greatest weight loss is achieved by people who are the most overweight at the beginning of exenatide therapy, while the weight-reducing effect continues at the same rate through 2 or more years of continued use [22–25]. Side effects of

Table 3. Summary of results for primary analysis of metabolic parameters with and without adjustment for body weight loss, mean (SEM).

Cardiometabolic parameter	Overall effect*	Effect beyond that of body weight loss alone*	Overall effect beyond that of body weight loss alone (%)
HDL cholesterol (%)	8.0	3.6	45
Triglycerides (%)	-14.0	-6.5	46
Fasting insulin (µIU/ml)	-2.74	-1.34	49
Adiponectin (µg/ml)	1.5 (0.2)	0.85	57
HbA _{1c} (%)	-0.67	-0.37	55

*Mean difference versus placebo at 1 year; $p < 0.001$ for all comparisons.

HDL: High-density lipoprotein.

Data taken from [17].

Table 4. Prescribing summary for orlistat, sibutramine and rimonabant.

Drug	Standard dose	Potentially useful in	Avoid in	Comments
Orlistat	120 mg three-times daily	Prediabetes, diabetes, raised LDL cholesterol, hypertension, pre-existing cardiovascular disease, patients who require long-term behavioral change	Malabsorption or chronic gastrointestinal disease	Prescribe concurrent multivitamin
Sibutramine	10–15 mg once-daily	Frequent snackers, nocturnal eaters, dyslipidemia (high triglyceride/low HDL cholesterol)	Uncontrolled hypertension, tachycardia, pre-existing cardiovascular disease	Monitor blood pressure and heart rate
Rimonabant	20 mg once-daily	Dyslipidemia (high triglyceride/low HDL cholesterol), diabetes, metabolic syndrome, hypertension	History of psychiatric illness, liver impairment	Monitor for mood disorders

HDL: High-density lipoprotein; LDL: Low-density lipoprotein.

exenatide are primarily gastrointestinal, including nausea, vomiting and diarrhea. However, they are mild to moderate and usually go away entirely after a few days or weeks. It is administered subcutaneously, twice-daily.

CCK is the first gut hormone that was recognized to inhibit food intake in animals, over 30 years ago [26]. The effect of CCK as an appetite suppressant seems to depend largely on its activation of CCK-1 receptors (formerly CCK-A) in the vagus nerve, suggesting a vagally mediated, endocrine mechanism that is triggered by food intake and subsequent stomach distension [27]. Although the results of preclinical studies with butabindide (which protects endogenous CCK from inactivation) [28] and GI181771X (a potent, full CCK-1 receptor agonist) were compatible with weight loss effects of CCK in animals, double-blind treatment with different GI181771X doses or matching placebo, together with a hypocaloric diet of patients with a BMI of 30 or over, or 27 kg/m² or more, did not reduce body weight and had no effect on waist circumference or other cardiometabolic risk markers, demonstrating that CCK-A by itself does not have a central role in long-term energy balance [29].

While the gut-acting weight-loss drug (orlistat) and the endocannabinoid receptor blocker (rimonabant) are relatively novel, the sympathomimetics have been in use for many years. Phentermine, diethylpropion, mazindol, benzphetamine and phendimetrazine are the main older-generation drugs of this class. They generally exert their weight-loss effect by decreasing appetite and increasing satiety and are recommended for short-term (up to 12 weeks) use only, as they are habit forming and individuals

may become physically and psychologically dependent on these medications after several weeks of continuous use. However, since the change in obesity management, according to which it is considered a chronic disease that requires long-term treatment, and since new adrenergic appetite suppressants with fewer side effects and authorization for long-term use have been developed, the older noradrenergic appetite suppressants are even less frequently used nowadays.

Bupropion, a dopamine- and norepinephrine-reuptake inhibitor, which is primarily used as an antidepressant and as a smoking-cessation aid, topiramate, which is anticonvulsant, and some SSRIs (fluoxetine and sertraline) have also been shown to suppress appetite, resulting in moderate weight loss in some patients following treatment of 6–12 months duration. However, owing to controversial results from other studies, at present they are not licensed as adjuncts to diet and exercise in weight-loss programs [30,31]. In addition, chitosan, a deacetylated chitin widely available as a dietary supplement that claims to aid weight loss, has been intensively investigated. A recent review that estimated its efficacy in weight loss concluded that it has only minimal effect on body weight, which is unlikely to be of any clinical significance [32]. Methylcellulose is the most commonly used bulk-forming laxative; however, although it is claimed to reduce intake by producing a feeling of satiety, there is little evidence to support its use in the management of obesity. Finally, according to Misato Kobayashi *et al.*, the bile acid-binding resins, such as cholestyramine and colestimide, which have been documented to improve lipids and glycemic profile in animal

models, can also ameliorate diet-induced obesity when given to overfeeding mice and, most importantly, without reducing food intake. The most probable method of action is by the reduction of fat absorption from the intestine. This fact could set bile acid-binding resins as novel therapeutic agents for the treatment of obesity, especially in Type 2 diabetic and dyslipidaemic patients; however, they are not yet licensed for such use [33].

Anti-obesity drugs in development

Since the need for effective anti-obesity therapies is currently unmet, as none of the currently used drugs seem to be the ‘magic’ solution to the obesity epidemic, achieving quick and permanent weight loss, while at the same time being cheap and safe for long-term or even lifelong use, intensive research is still in progress for the development of novel, more effective drugs.

Leptin is considered the main long-term afferent signal that informs the CNS of the energy-stores balance, so that the necessary adjustments in feeding behavior can be made for efficient matching between energy intake and expenditure and the maintenance of the energy stores. An increase in body fat mass leads to an elevation in the concentration of leptin in the blood, inducing a negative energy balance, which tends to return body fuel stores to the set point. Leptin binds to the ‘satiety’ center (ventral medial nucleus) of the hypothalamus and induces the sensation of satiety by inhibiting the activity of NPY- and AgRP-containing hypothalamic neurons that induce hunger, while at the same time increasing the activity of others that induce satiety, such as those expressing the α -melanocyte-stimulating hormone (α -MSH). Administration of recombinant leptin in obese individuals with a mutated leptin gene proved to be of great benefit, resulting in excessive weight loss, while a dose–response relationship with weight and fat loss was observed with subcutaneous recombinant leptin injections in both lean and obese subjects [34], supporting a weight-reducing effect of exogenous leptin in some obese subjects who already have elevated endogenous serum leptin concentrations.

In addition to the CB1 receptors of the endocannabinoid system, many other central receptors and biochemical pathways are being investigated as potential targets for future anti-obesity drugs. The central melanocortin pathway, which includes a group of neurons located in the arcuate nucleus of the hypothalamus and

which possesses a key role in appetite control and energy homeostasis regulation, is currently being intensively studied. Several agonists and antagonists of its receptors are assessed for their weight-loss efficacy. Melanocortin-4 receptor agonists, as well as ghrelin [35], NPY, PPY [36] and melanin concentrating hormone antagonists, are some of them [25]. Animal data support the beneficial effect on weight management, by the use of such agonists and antagonists, but we are still a few years away from their use in clinical practice [37].

The afferent signals from the gut are a very important part of the energy homeostasis system. The effectiveness of exogenous pancreatic polypeptide (PP) as an appetite suppressant has been intensively investigated in recent years [38]. Administration of PP as a potential obesity treatment has the advantage that it mimics the safe and natural way in which the body suppresses appetite. This hypothesis is supported by the fact that patients with benign PP-secreting tumors, who had elevated levels of the hormone for more than 10–15 years, did not show any side effects, thus suggesting that PP administration may be useful for weight management. If the results of this research support the effectiveness of PP in weight loss, this may lead to a treatment within 5–8 years, in an oral or injectable formula.

In recent years, the role of 11- β -hydroxysteroid dehydrogenase 1 (11 β -HSD1) in the development of visceral obesity has been intensively investigated. According to recent human studies, its expression was increased twofold in central fat and was positively correlated with waist circumference and insulin resistance. These results support its detrimental effect on the energy stores metabolism, paving the way for the development of drugs that may target the 11 β -HSD1 gene’s expression in visceral adipose tissue [39].

The concept of adding something to food to provide health benefits is not new. The importance of diet-induced thermogenesis in the resistance to diet-induced obesity has been well documented [15,40]. Further work is needed to identify tissues and molecular pathways mediating diet-induced thermogenesis (DIT), to develop foods that might cause significantly higher thermogenesis. The determination of differences in DIT according to a meal’s macronutrient composition, as well as the role of the medium-chain triacylglycerols in thermogenesis, irrespective of the meal components, is only the beginning of a very promising aspect of recruiting functional foods in weight-loss strategies in the future.

Conclusion

Obesity is not a recent phenomenon, but the epidemic of obesity is. Widely spread in modern human societies, but also in developing countries, it is estimated that approximately 315 million people worldwide meet the WHO criteria of obesity. Associated with several potentially life-threatening cardiovascular and metabolic disorders, as well as with significant morbidity, mortality and impaired quality of life, obesity is considered a chronic disease that requires long-term or even lifelong treatment. On the other hand, even moderate steady weight loss results in significant health benefits. Calculations made for NICE on the cost-effectiveness of current anti-obesity drugs suggest a figure of £15,000–30,000 per quality-adjusted life year gained [5]. The combination of diet, exercise and behavior therapy remains the gold standard of weight-loss programs, while pharmacological intervention is recommended in selected patients in whom lifestyle modifications have failed. Although uncertainty

regarding the safety and effectiveness of current drug therapies still remain, the long-term pharmacological approaches seem to be promising not only for weight loss, but also for maintenance of weight loss. Orlistat, sibutramine and rimonabant are currently the only anti-obesity drugs licensed for long-term use, while they also demonstrate beneficial effects on several surrogate cardiovascular markers further to weight loss; however, interpretation is limited owing to high attrition rates (30–40% on average) and lack of long-term outcome data [41].

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending or royalties.

No writing assistance was utilized in the production of this manuscript.

Executive summary

- Obesity is major health problem with significant comorbidities.
- The use of drugs in weight management has been an area of great interest for many years.
- The research target is the development of efficient and safe drugs for long-term or even life-long usage.
- The recent years, the short-term acting drugs have been replaced by long-term acting drugs.
- Currently, the most widely used anti-obesity drugs are those that reduce the absorption of ingested fat (orlistat) and those that suppress appetite (sibutramine and rimonabant).
- Most randomized, controlled trials are compatible with significant weight loss by the use of these drugs; however, interpretation is limited owing to high attrition rates (30–40% on average).
- The gut is considered of great importance in the regulation of the energy-balance system.
- The potential role of drugs that mimic (e.g., GLP-1, PYY and so on) or antagonize gut-derived hormones (e.g., ghrelin antagonist) is being investigated.
- Other drugs that directly affect the appetite centre (e.g., melanocortin-4 receptor agonists) are only a few years away from the market.

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