Recent and Future Drugs for the Treatment of Obesity

Luc F. Van Gaal, Ilse L. Mertens and Ivo H. De Leeuw

University Hospital Antwerp, Belgium

INTRODUCTION

Obesity is becoming increasingly common and is recognized as a major public health problem worldwide (1). The prevalence of obesity continues to increase in the majority of affluent societies. In most European countries, the prevalence of obesity (body mass index (BMI) > 30 kg/m²) is roughly between 10 and 20% among middle-aged people, and over the last 10–15 years the overweight and obese population has increased by almost 15%, mainly in young adults and adolescents.

There is, in addition, growing evidence that obesity—central adiposity in particular—has an important impact on predisposing risk factors for coronary heart disease, namely dyslipidaemia, glucose intolerance, insulin resistance and elevated blood pressure. Reversal of these ‘obesity associated’ metabolic abnormalities is one of the most important targets in the current clinical management of obesity (2,3).

The aetiology of obesity is multifactorial and is the result of a complex interaction between genetic, environmental (predominantly dietary) and psychosocial factors. Due to this complexity, obesity is difficult to treat and comprehensive treatment programmes combine diet, exercise and behavioural therapy.

Although dietary approaches and lifestyle adaptation remain the cornerstones of obesity therapy (4,5), long-term success is extremely disappointing, despite the variety of dietary manipulations that have been proposed, ranging from scientifically studied diet plans (calorie restriction, fat restriction only, very low calorie diet (VLCD)) to the most ridiculous approaches, the long-term maintenance of clinically significant weight loss (5–10% of initial body weight) remains rare (4). In recent years a lot of attention has been paid to the role of pharmacotherapy as an additional treatment option with new drugs being marketed and exploration of new biochemical pathways and new pharmacological intervention potentials.

New clinical guidelines for the management of obesity have been published by different organizations such as the North American Association for the Study of Obesity (6), the Institute of Medicine (7), the US National Institutes of Health (8), the Scottish Intercollegiate Guidelines Network (9) and the Royal College of Physicians of London (10). In these documents a modest weight loss (5–10% of initial weight) and weight maintenance is recommended, rather than targeting on ideal weight.

It has previously been shown that an intentional modest weight reduction may lead to a marked improvement in cardiovascular risk factors and a substantial reduction—up to 20–25%—in comorbidity (11,12) (Table 31.1). Large-scale 1- and 2-year placebo-controlled studies with orlistat, sibutramine and dexfenfluramine have shown that a mean weight loss of 10% can be reached with these compounds (13). Weight loss is not the only goal of
Table 31.1  Risk factors that can be reduced by at least 10% by drug-induced weight changes

- Hypertension
- Glucose intolerance
- Hypercholesterolaemia
- Hypertriglyceridaemia
- Low HDL cholesterol levels
- Haemostatic/fibrinolytic parameters (FVII, PAI-1)

HDL, high density lipoprotein; FVII, haemostatic factor VII; PAI-1, plasminogen activator inhibitor 1.

Table 31.2  Characteristics of an ideal anti-obesity agent

- Produce weight (fat) reduction in a dose-dependent manner
- Proven to be safe without major side effects
- Effects should be long lasting
- By preference be active via oral administration
- May not show any addictive properties and/or toxicity
- By preference reduce the amount of visceral fat
- Inexpensive

obesity treatment: improvement in comorbidities, such as diabetes, hypertension and dyslipidaemia, is an important second endpoint in these studies. Some anti-obesity agents have even proven to have a positive effect on these comorbidities independent of weight loss. Dexfenfluramine, a serotoninergic compound, seems to have a blood pressure lowering effect, independent of weight loss, which is probably mediated through a decrease in noradrenergic activity (14,15). Orlistat, a selective inhibitor of gastric and pancreatic lipase, has been shown to produce a significant decrease in lipids that is greater than can be expected from weight loss alone (16).

For morbid obesity, however, the 10% weight loss option may be inappropriate and larger weight loss may be necessary. The results of the large, prospective, Swedish Obese Subjects (SOS) Study on surgical intervention will most probably give more insights and answers to this question (17). The place and appropriateness of surgery will be reviewed in detail in Chapter 34.

For several decades pharmacological treatment of obesity had a negative reputation most likely due to the abuse of thyroid hormones, amphetamines, digitalis and diuretics. In 1997, fenfluramine and dexfenfluramine were withdrawn from the market due to reports of pulmonary hypertension (18) and valvular heart disease (19) in patients treated with fenfluramine and phentermine. These events led some people to suggest that drugs are not appropriate for the treatment of obesity. Recently, however, obesity has been recognized as a chronic disease (8) for which no cure is available yet (20). This implies that short-term treatment is not enough for most obese patients and that obesity should be treated as any other chronic disease—such as type 2 diabetes and hypertension—requiring lifelong treatment in which pharmacological agents could play an important role (21). The search for anti-obesity drugs which are effective and safe for chronic use is an important challenge.

GENERAL PHARMACOLOGICAL ASPECTS

Large-scale, long-term (up to 2 years) studies have demonstrated that pharmacological agents (dexfenfluramine previously, more recently orlistat and sibutramine) are able to induce significant weight loss in conjunction with dietary approaches, and important reduction of comorbidities as well. The majority of these drugs allow maintenance of the reduced body weight for at least 1–2 years. The weight loss that can be attributed to these drugs is in general modest, in accordance with the 10% weight loss option, but will be accompanied by a reduction of around 25% of most of the well-known comorbid conditions.

Although the ideal weight loss drug does not exist yet, a series of characteristics should be considered in qualifying a molecule for human use (Table 31.2). It is important that drugs are effective in reducing body fat, visceral fat in preference, without displaying any major health risks (13,22). In addition, the effect of the drug should be long lasting. In this context, the effect of the drug on the maintenance of achieved weight loss is as important as the initiation of weight loss. It is not the case that a drug designed for weight loss does not have any effect once a phase of weight stabilization after weight loss has been reached. In this situation, discontinuation of the drug treatment will most probably result in weight regain (23).

Overweight and obesity are a consequence of an energy imbalance between energy intake and expenditure: the human body is as an interface of environmental and biological factors, influenced by this energy balance. The components—both environmental and biological—that may interfere with this balance, should be modulated during obesity management.
Anti-obesity drugs can be classified according to their mechanism of action on energy balance (2, 24). Considering these components involved in the regulation of body weight, three different mechanisms may be used to classify pharmacological treatment of obesity (Table 31.3).

Contrary to previous reviews on drug therapy, dealing with a classification based on these mechanisms of action, this chapter will follow the experience with drug therapy that has been accumulated in the past, that is happening at present and that will come in the following years. Only drugs that reduce food intake and influence nutrient partitioning are currently available; drugs that stimulate energy expenditure, such as β3 agonists, are still under development (25).

<table>
<thead>
<tr>
<th>Table 31.3 Classification of drugs according to their effect on energy balance</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Drugs involved in appetite behaviour (nutrient intake), mainly appetite suppression and satiety enhancement</td>
</tr>
<tr>
<td>• Drugs involved in increasing energy expenditure, mainly thermogenic properties</td>
</tr>
<tr>
<td>• Drugs affecting metabolism or nutrient partitioning</td>
</tr>
</tbody>
</table>

WHO SHOULD BE MANAGED PHARMACOLOGICALLY?

The decision concerning who to treat should be based on an individual assessment of all available factors and the appropriate indications for treatment need to be carefully considered. The inherent risk of the disease must be assessed in relation to the risks of treatment (26).

It is clear that classical weight loss techniques do not produce a satisfactory long-term outcome for most obese patients (27). Pharmacotherapy could be valuable in addition to classical weight loss therapy both in achieving initial weight loss and in maintaining weight loss.

The Clinical Guidelines for evaluation and treatment of obesity, released by the National Institutes of Health (8), recommend that weight loss drugs should only be used as part of a comprehensive programme which includes dietary adaptation, physical activity and behavioural and psychological support. Recent data have shown that regular scheduled visits including dietetic and physical activity advice add a significant additional weight reduction to that obtained with drug therapy combined with a calorie restricted diet (28). This shows that the specific approach to the non-pharmacological components of the weight loss programme plays an important role in the final outcome of the programme. To be considered for pharmacotherapy, candidates should have a BMI ≥ 30 without risk factors, or a BMI of ≥ 27 associated with the well-known—mostly metabolic—obesity-related health and risk problems. Risk factors and diseases considered important enough to warrant pharmacotherapy for patients with a BMI of 27 to 29.9 include hypertension, dyslipidaemia, coronary heart disease, type 2 diabetes, and sleep apnoea (8). Only patients that have failed to lose weight on a regular weight loss programme of diet, exercise and behaviour therapy can be considered for drug therapy. However, although not endorsed by American and European drug agencies, subjects with a recent onset of obesity and a rather sudden weight gain of 10–15 kg, might qualify for safe pharmacological treatment as well.

Patients selected for drug therapy should be given complete information about the drug, the potential adverse effects, and long-term efficacy (29). Patients should know that not all will respond to drug therapy and that it is important to visit the doctor and dietician on a regular basis. Close medical monitoring for adverse effects while using the medications is important. Understanding the risks and benefits of anti-obesity medications is critical in the development of effective approaches for weight management and obesity prevention.

Recently much attention has been paid to the identification of factors predicting the outcome of weight loss programmes. Different papers have described the impact of biological, psychological and behavioural characteristics such as sex (30), race (30), pre-treatment weight (30,31), initial weight loss (31), 24-hour energy expenditure, % fat oxidation, plasma dihydrotestosterone, postprandial noradrenaline concentration (32), binge eating disorder (33) and previous weight loss attempts (30,34).

In clinical trials evaluating drug therapy the initial weight of the patients, weight loss achieved during the run-in phase of the study and/or first month of the study, fat distribution and genetic factors could play a role in the determination of the final outcome for the individual patient. Genetic polymorphisms linked to the mechanism of action...
of the drug could play an additional role. In a study
with dexfenfluramine high compliance with the
drug regimen and a positive family history of obes-
ity were predictive of final weight loss. Previous
failure to lose weight did not have any effect on
outcome (35). In a 24-week trial including
1047 patients treated with sibutramine, weight loss
achieved at week 4 was predictive for weight loss
achieved after 24 weeks of treatment (36). An analy-
sis of pooled data from two European multicentre
trials with orlistat revealed that, in orlistat-treated
patients, mean weight loss was greater after 1 year
in patients who lost \( \geq 5\% \) of body weight after 12
weeks of treatment than in those who lost \(< 5\% \)
(37).

From a clinical point of view, identifying the
characteristics of those patients most likely to bene-
fit from therapy will make it easier to match the
individual patient to the most effective treatment
for this patient and prevent unnecessary drug pre-
scription. The Clinical Guidelines from the Nation-
al Institutes of Health (8) advise discontinuing drug
therapy if the patient fails to lose \( \geq 2\) kg after 4
weeks of treatment. The Royal College of Phys-
icians of London (10) has recommended 5% weight
loss after 12 weeks of treatment as the goal for
continued treatment.

PREVIOUS EXPERIENCE WITH
ANTI-OBESITY DRUGS (Table 31.4)

**Drugs Affecting Energy Intake**

Use of anorectic drugs usually results in a reduction
of nutrient intake, leading to a loss in body weight
and fat mass in particular; this effect is usually
obtained by a decrease in appetite. Anorectic drugs
can play a useful role in an overall weight reduction
programme, but should only be prescribed as part
of such a programme, including dietary and behav-
ioral advice.

**Catecholaminergic Anorectics**

Most of the previously available appetite-suppress-
ing drugs, except mazindol, are derivatives of
phenylethylamine (amphetamine, phenmetrazine,
amfepramone or diethylpropion, phentermine,
phenylpropanolamine). Noradrenergic drugs re-

<table>
<thead>
<tr>
<th>Table 31.4</th>
<th>Drugs that have been used in the treatment of obesity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Catecholaminergic drugs</td>
<td>Serotonergic drugs</td>
</tr>
<tr>
<td>Amphetamine</td>
<td>Fenfluramine</td>
</tr>
<tr>
<td>Phenmetrazine</td>
<td>Dexfenfluramine</td>
</tr>
<tr>
<td>Diethylpropion</td>
<td>(Fluoxetine)</td>
</tr>
<tr>
<td>Phentermine</td>
<td></td>
</tr>
<tr>
<td>Phenylpropanolamine</td>
<td></td>
</tr>
<tr>
<td>Mazindol</td>
<td></td>
</tr>
</tbody>
</table>

**Fenfluramine and Dexfenfluramine**

The serotoninergic drugs fenfluramine and dexfen-
fluramine are metabolized to \( d \)-norfenfluramine,
which enhances serotonin release from the neurons
and acts as an agonist for serotonin (5-HT) recep-
tors. In addition, dexfenfluramine acts also by inhib-
iting reuptake of serotonin into the neurons (24).
The clinical efficacy of fenfluramine and dexfen-
fluramine \((2 \times 15\,\text{mg/day})\) has been demonstrated
in trials of short and long duration conducted over
the past 30 years (38). In contrast to catech-
olaminergic drugs, serotoninergic compounds
should be used continuously and do not exert
stimulant or sympathomimetic activities or induce
tolerance.

However, several reports of pulmonary hyperten-
sion and, more recently, of cardiac valvular abnor-
malities have been published (18,19). In 1996, a
case-control study conducted by the International
Primary Pulmonary Hypertension Study Group
(18) showed that the use of fenfluramine derivates
for 3 months or more was associated with a 23-fold increase in the risk of primary pulmonary hypertension, a rare but often fatal disorder. One year later, in 1997, a paper by Connolly et al. (19) reported on the association between treatment with the fenfluramine–phentermine combination and valvular heart disease. Since this first publication by Connolly et al. (19), new studies have been published on the association between appetite suppressants and valvular heart disease (39–41). Weissman et al. (41) performed echocardiography after 72 days of treatment with dexfenfluramine and found cardiac valve abnormalities in 6.9% of treated patients compared to 4.5% in the placebo groups. Jick et al. (39) performed a population-based follow-up study over 4 years of patients treated with dexfenfluramine (n = 6532), fenfluramine (n = 2371) and phentermine (n = 862) and found five new cases of valvular disease in the dexfenfluramine group and six new cases treated with fenfluramine. Finally, Kahn et al. (40) studied the prevalence of cardiac valve insufficiency in patients taking dexfenfluramine (13%), dexfenfluramine and phentermine (23%), or fenfluramine and phentermine (25%). The results from these studies seem to confirm the earlier findings of Connolly et al. (19). However, the studies show differences in the magnitude of the risk that may influence the subsequent clinical significance. The difference in results could be due to methodological differences such as the type of anorectic used or lack of baseline echocardiographic studies, duration of treatment and the method of diagnoses (42). The precise mechanism linking the use of fenfluramine derivatives to valvular heart disease is not yet completely understood. One of the hypotheses relates to the serotonin-releasing effect of the drugs. Serotonin could have an effect on the cardiac valves, as seen in the carcinoid syndrome which is associated with high serotonin levels due to a serotonin-secreting neoplasm (43).

**Fluoxetine**

Fluoxetine is a well-known antidepressant drug which acts by inhibiting the reuptake of serotonin. In contrast to fenfluramine, fluoxetine does not stimulate serotonin release and enhances synaptic serotonin concentration by blocking its reuptake (44). This characteristic may explain why no cases of pulmonary hypertension or cardiac valvular abnormalities have been described so far with this compound despite its very wide utilization as an antidepressant drug. Fluoxetine is an effective anorectic agent promoting weight loss: this has been confirmed in obese subjects, even in the absence of depression. This effect was also seen in obese diabetic subjects, as shown in a multicentre study (45). However, the dose effective to reduce body weight is higher (60 mg/day) than that generally used in the treatment of depression and the effect may be transient as a significant weight regain has been reported after 6–12 months of treatment (45).

### Drugs Affecting Energy Expenditure

Much less experience exists in the field of clinical obesity with drugs that increase energy expenditure, thermogenesis in particular. Pharmacological stimulation of thermogenesis would be a rational target for anti-obesity action, however (46). The largest experience exists with the ephedrine–caffeine combination therapy, which may increase metabolic rate and delay norepinephrine degradation (47). Cardiovascular side effects, often seen with high doses of ephedrine, have limited the widespread use of this kind of approach. Also the clinical application of the β3-adrenergic receptor agonists, an interesting category of drugs involved in increasing thermogenesis and metabolic rate, has been very disappointing and mostly unsuccessful in clinical trials until now, despite their promising and sometimes even spectacular results in rodents (48).

### RECENT NEW EXPERIENCE WITH ANTI-OBESEITY DRUGS

#### Centrally Active Drugs: Sibutramine

Sibutramine (Figure 31.1) is a centrally acting agent that dose-dependently inhibits serotonin and noradrenaline reuptake (49). Sibutramine’s action in inhibiting the reuptake of serotonin enhances satiety and thus decreases energy intake (50). By inhibiting noradrenaline reuptake, sibutramine enhances sympathetic outflow, including to brown adipose tissue, leading to increased thermogenesis and thus increased energy expenditure.
Sibutramine

![Structure of sibutramine and orlistat](image)

Figure 31.1 Structure of sibutramine and orlistat, two recent drugs developed for the treatment of obesity

The sibutramine parent molecule is efficiently absorbed from the gastrointestinal tract and undergoes an extensive first-pass metabolism. Hepatic metabolism of the parent molecule by the cytochrome P450 enzyme system leads to the formation of two active metabolites, termed metabolite 1 and metabolite 2 (51). Metabolite 1 is a secondary amine and metabolite 2 is a primary amine. These two metabolites mediate the pharmacological activity of the sibutramine molecule. Further metabolism yields inactive glucoronidases, which are excreted in the urine. As metabolites 1 and 2 have half-lives of 14 h and 16 h, respectively, sibutramine can be given as a once-daily dose (51).

The pharmacological activity of sibutramine does not appear to be a result of increased serotonin release; this differentiates it from the actions of dexfenfluramine, a predominantly serotonin-releasing compound, and dexamphetamine, which predominantly releases dopamine and noradrenaline. This might explain why sibutramine has not been associated with cardiac valve insufficiency. This was illustrated in a study of 210 obese patients with late-onset diabetes treated with sibutramine or placebo, in which the rate of valve problems was 2.3% in the sibutramine group and 2.6% in the placebo group (52). In *in vitro* studies as well as trials conducted in animals and humans, sibutramine and its metabolites also showed no significant potential for inducing dopamine release, unlike dexamphetamine. This may account for the lack of abuse potential with sibutramine.

Given the role of the liver in sibutramine metabolism, administration of sibutramine to patients with severe hepatic disease is inadvisable, at least until further information becomes available. It would also seem wise to exercise caution regarding the use of sibutramine in conjunction with other drugs requiring the cytochrome P450 enzyme system (53).

Both pre- and postsynaptic α2-adrenoceptors in brain tissue appear to be rapidly downregulated by sibutramine. The effect of sibutramine on clonidine-induced hypoactivity and mydriasis was used in mice to measure the activity of the drug at, respectively, pre- and postsynaptic α2-adrenoceptors (54). Sibutramine significantly reduced these activities after 3 days (*P* < 0.01 vs. placebo) with a greater effect on post- than presynaptic α2-adrenoceptors (42 vs. 15% reduction after 14 days' sibutramine administration) (55). Daily administration of sibutramine (3 mg/kg) reduced the total number of β-adrenoceptors in rat cortex by 23% after 3 days and by 38% after 10 days; this was exclusively via reduction of the β1-adrenoceptor subset (56). Data regarding the effects of sibutramine on food behaviour via a variety of α- and β-adrenergic receptors seems conflicting. Studies of the hypophagic effects of sibutramine support an α-adrenergic and β1-adrenergic but not β2-adrenergic effect of the drug. There are few published primary data on the effects of sibutramine on β3-adrenoceptors (55,57).

Sibutramine has no effect on the binding affinity or number of dopamine D1 (58,59) or dopamine D2 receptors (60) in rat striatal membranes. Sibutramine’s weight-reducing efficacy is comparable with that of earlier appetite-suppressant noradrenergic and serotonergic compounds (55).

Most clinical trials in obese patients combined sibutramine administration with a reduction in calorie intake, an increase in daily physical activity and advice on eating behaviour (61,62). Indeed, the drug should be administered in conjunction with a reduced calorie intake. Most clinical trials investigating the effects of sibutramine followed a similar protocol: a 1- to 3-week single-blind placebo run-in period followed by a double-blind placebo-controlled treatment period. The single-blind run-in period observed the effects of diet and/or behavioural changes. The treatment phase lasted 8–52 weeks and was commonly followed by a second single-blind placebo period to assess weight change after drug discontinuation (55).

A report of a 24-week dose-ranging study, recent-
ly published, indicated that sibutramine administered once daily for 24 weeks in the weight loss phase of treatment for uncomplicated obesity produced dose-related weight loss and was well tolerated (36), leading to a mean weight loss of up to 9–10% from baseline weight. With 10 mg sibutramine, almost 60% of patients could obtain 5% weight loss and 17.2% reached the clinically important 10% weight loss (36) (see also Figure 31.2).

Long-term clinical trials indicate that sibutramine given for 6 months induces a significant dosage-dependent reduction in body weight, which for dosages ranging from 10 to 20 mg/day was 3 to 5 kg greater than the loss of body weight with placebo.

Following a very low calorie diet, sibutramine-treated patients lost more weight than placebo-treated patients during the subsequent 12 months. A substantial tendency to regain weight was observed in the placebo group, compared with additional weight loss in the sibutramine group (66). This time-course of weight loss is similar to that observed in the 20 long-term weight-reduction studies reviewed by Goldstein and Potvin (67). Sibutramine helped greater proportions of patients to maintain \( \geq 100\% \), \( \geq 50\% \), or 25% of weight loss following a very low calorie diet and was associated with decreases in waist circumference (66).

The STORM trial, a 2-year sibutramine trial of obesity reduction and maintenance, and presented at the most recent European Congress (68), assessed the usefulness of the drug in maintaining substantial weight loss in a randomized controlled double-blind trial. Over 600 obese individuals were studied in eight European centres for a 6-month period of weight loss with sibutramine, combined with an individualized 600 kcal deficit programme based on measured basal metabolic rates. Seventy-seven per cent of patients with > 5% weight loss after 6 months were randomized 3:1 to sibutramine (10 mg/day) and placebo groups to study weight maintenance over a further 18 months. Sibutramine was increased up to 20 mg/day if weight regain occurred. Initially weight loss progressed to a total of \(-11.3\) kg after 6 months. After randomization the placebo group regained weight to \(-4.7 \pm 7.2\) kg at 2 years; the sibutramine group only showed slight weight regain to \(-10.2\) kg \(\pm 9.3\) kg at 2 years (Fig-

![Figure 31.2](image.png)

**Figure 31.2** Percentage of patients obtaining a weight loss of 10% or more of baseline weight in clinical trials after 1 year of treatment with dexfenfluramine (63), orlistat (64) and sibutramine (65). Adapted from Scheen and Lefèvre (13)
Marked and sustained falls occurred with sibutramine over the first 6 months in cardiovascular risk factors such as triglycerides, very low density lipoprotein (VLDL), insulin, C-peptide and uric acid. An important finding was the rise in high density lipoprotein (HDL) cholesterol in the second year with overall increases of 20.7% (sibutramine) and 11.7% (placebo). Adverse events were modest: only 20 (3%) patients were withdrawn with blood pressure problems (68).

Sibutramine is, in some preliminary studies at least, also able to stimulate thermogenesis (69) and to reduce significantly the amount of visceral fat (70). Energy expenditure was significantly increased during the 5-hour period after administration of sibutramine 30 mg compared with placebo in healthy volunteers (71). Energy expenditure, as measured by indirect calorimetry, was increased during the fasted and the fed states by 152 and 34% versus placebo, respectively. These sibutramine-induced increases were accompanied by increases in plasma catecholamines and glucose concentrations, heart rate and diastolic blood pressure. Resting energy expenditure was decreased from baseline values by about half as much with sibutramine 10 mg as with placebo (by 5.3 vs. 9.4%; not statistically significantly different) in obese female patients (55,72). It is thought that this smaller decrease in resting energy expenditure may contribute to the long-term maintenance of weight seen with sibutramine (55).

As reported previously, sibutramine (10 mg), is associated with an increase in heart rate (3 to 6 beats/min) and systolic blood pressure (2 mmHg). This effect of sibutramine is in keeping with its noradrenergic action. This effect seems to be attenuated the more (visceral) fat is lost. The most frequently reported adverse events included dry mouth, anorexia, constipation, insomnia, dizziness and nausea.

**Pre-absorptive Nutrient Partitioning: Orlistat**

Due to their high energy content and low potential for inducing satiety, high fat diets are very conducive to weight gain, particularly in individuals who are relatively inactive. Indeed, humans are much more likely to become obese through the excessive consumption of dietary fat than by excess consumption of carbohydrate (73). It is rational, therefore, to decrease the proportion of fat, as well as the total number of calories. By reducing fat absorption after ingestion, a continued calorie deficit may be maintained more easily over the long term than by dieting alone.

Orlistat, the first of a new class of agents specifically designed for the long-term management of obesity, is a chemically synthesized derivative of lipstatin (a natural product of *Streptomyces toxyticus*). Orlistat is an inhibitor of gastric and pancreatic lipases, which are instrumental in the digestion
and absorption of fat from the gastrointestinal tract. Inhibition of lipase activity has the effect of decreasing fat absorption by 30%, independent of the amount of fat intake, and increasing the excretion of triglycerides in the faeces (74,75).

In vitro studies showed that the concentration of orlistat required to produce 50% inhibition of lipases present in human duodenal juice was low (76). The actual pharmacodynamic interaction between lipase and orlistat is complex (77). The extent of enzyme inhibition by the drug is time and concentration dependent (76). Orlistat is highly lipophilic and distributes into the lipid phase of an aqueous/oil partition model. In vitro experiments suggest that inhibition of pancreatic lipase by orlistat is practically irreversible (76). The effects of orlistat on hydrolases other than lipases have been investigated in vitro. The drug had no effect on other enzymes such as phospholipase or amylase and a minimal effect on trypsin (16,76).

The systemic absorption of orlistat is minimal. After oral administration of a single dose of 360 mg $^{14}$C-labelled orlistat to healthy or obese volunteers, peak plasma radioactivity levels were reached approximately 6 to 8 hours after the dose (78,79). Plasma concentrations of intact orlistat were small, indicating negligible systemic absorption of the drug (79). Pooled data from five long-term (6 months to 2 years) clinical trials with orlistat 180 to 720 mg/day in obese patients indicated that there was a dose-related increase in plasma concentrations of orlistat in several clinical studies. However, these plasma concentrations were generally below the level of assay detection (16).

No pharmacodynamic or pharmacokinetic interactions were observed with orlistat 360 mg/day and warfarin (80) or glyburide (81) in healthy volunteers or with pravastatin in patients with mild hypercholesterolaemia (82). No pharmacokinetic interactions were reported with orlistat and digoxin (83), nifedipine (84) or phenytoin (85). Orlistat did not interfere with oral contraceptive medication in healthy women (86). Orlistat had no clinically significant effects on the pharmacokinetics of captopril, nifedipine, atenolol or frusemide in healthy volunteers (85). Short-term treatment with orlistat had no effect on ethanol pharmacokinetics, nor did ethanol interfere with the ability of orlistat to inhibit dietary fat absorption in healthy male volunteers (16,87).

A number of short-term trials have revealed that orlistat promotes weight loss and improves hypercholesterolaemia in obese patients. The weight-reducing effect of orlistat was initially shown in a short-term multiple dose study involving almost 200 healthy, obese subjects. Weight reduction was statistically significant in those subjects receiving orlistat 120 mg three times daily (tid) compared to those dieting alone (74,88). Initial studies on healthy volunteers have shown that the maximum amount of fat excreted in the faeces following doses of orlistat at 400 mg/day is approximately 32% of fat ingested. Orlistat (10–20 mg tid) has also been shown to improve the lipid profile of non-obese and obese patients with primary hyperlipidaemia.

A European dose-ranging study, conducted by our own research group, indicated that among 676 obese male and female subjects orlistat treatment resulted in a dose-dependent reduction in body weight, with orlistat 120 mg tid representing the optimal dosage regimen (89).

The efficacy of orlistat has meanwhile been evaluated in obese patients aged 18 to 78 years in seven randomized, double-blind, placebo-controlled multicentre US and European trials of 12 weeks to 2 years duration. Generally, patients were obese but otherwise healthy although one trial evaluated the efficacy of orlistat in obese patients with type 2 diabetes mellitus (90). Obesity was classified according to BMI; mean BMI values were 31 to 36 kg/m². Patients were also prescribed a hypocaloric weight loss diet (500 to 800 kcal/day deficit) consisting of 30% of calories as fat, 50% as carbohydrate, 20% as protein, and a maximum of 300 mg per day of cholesterol (16).

In the 2-year randomized double-blind placebo-controlled trial with orlistat conducted recently by Sjöström and colleagues, 38.8% of patients treated with orlistat lost > 10% of their initial body weight versus 17.7% in the placebo group (64) (Figure 31.4). This indicates that orlistat can be considered as a valuable adjunct to dietary therapy in patients on weight maintenance.

However, as emphasized by the authors, ‘the use of orlistat beyond 2 years needs careful monitoring with respect to efficacy and adverse events’ (64).

A comparable 2-year orlistat trial, conducted in 18 US research centres, confirmed the Sjöström data: orlistat treatment in addition to dietary approaches promotes significant weight loss, decreases weight regain and improves some obesity-related disease risk factors. During the first year
obesity treated subjects lost approximately 3 kg more weight than did placebo subjects (91). Also in subjects with type 2 diabetes, a beneficial effect of orlistat has been proven, despite the usually very limited successes with weight loss in diabetics (90). The results showed a weight loss superior in diabetics compared to placebo, improvement of metabolic control and a decrease in the concomitant ongoing anti-diabetic therapy (90).

The most reported adverse effects consisted of abdominal pain, liquid stools, faecal incontinence with oily stools, nausea, vomiting and flatulence, but these symptoms were in general mild and transient. There was also some trend towards a decrease in lipid-soluble vitamin levels, but only the decrease in vitamin E levels was statistically significant, while remaining within normal ranges.

**Figure 31.4** Mean percentage change in body weight in a 2-year trial with orlistat studying weight loss and prevention of weight regain in obese patients. In the first year patients were assigned double-blind to treatment with orlistat 120 mg tid or placebo together with a 600 kcal deficit diet. In the second year patients were reassigned to orlistat or placebo with a eucaloric diet. * Chi-square $P < 0.05$ (vs. placebo). Adapted from Sjöström et al. (64)

**Post-absorptive Nutrient Partitioning:**
**Testosterone and Growth Hormone**

Another potential target for drug treatment is modulation of metabolic processes. Although not yet tested in large clinical trials, testosterone and growth hormone therapy have been shown to have positive effects on body fat and body fat distribution. Studies evaluating the effect of growth hormone replacement therapy in multiple pituitary hormone deficiencies (92,93) or isolated growth hormone deficiency (94,95) show that growth hormone is an important regulator of intra-abdominal fat mass. Recently two studies showed that growth hormone treatment reduces the size of total abdominal fat (95) subcutaneous fat (94), as well as intra-abdominal fat mass (94,95). Márin et al. (96) treated 23 middle-aged abdominally obese men with oral testosterone supplements for 8 months. Visceral fat mass, measured by computerised tomography, decreased significantly without a change in body mass, subcutaneous fat mass or lean body mass.

**EFFECTS OF PHARMACOLOGICAL TREATMENT ON WEIGHT MAINTENANCE** (Table 31.5)

Long-term results of weight loss programmes are often disappointing. This was shown by the work of
Table 31.5  Long-lasting effects of drug therapy on weight: 1- and 2-year trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Duration (years)</th>
<th>Dose (mg/day)</th>
<th>Subjects (n)</th>
<th>Weight change (kg) Drug/Placebo</th>
<th>Weight change (%) Drug/Placebo</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dexfenfluramine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Guy-Grand et al. (63)</td>
<td>1</td>
<td>30</td>
<td>404/418</td>
<td>−9.8/−7.1</td>
<td>−10.3/−7.2</td>
<td>INDEX trial; Diet dependent on usual practice of each centre</td>
</tr>
<tr>
<td>Andersen et al. (99)</td>
<td>1</td>
<td>30</td>
<td>21/21</td>
<td>−10/−9</td>
<td>−10.8/−8.4</td>
<td>Part of INDEX trial; Diet: VLCD</td>
</tr>
<tr>
<td>Mathus-Vliegen et al. (100)</td>
<td>1</td>
<td>30</td>
<td>36/39</td>
<td>−10.7/−8.0</td>
<td>−9.6/−7.3</td>
<td>Part of INDEX trial</td>
</tr>
<tr>
<td>Pföhl et al. (101)</td>
<td>1</td>
<td>30</td>
<td>24/24</td>
<td>−10.9/−9.6</td>
<td>−11.2/−9.1</td>
<td>Part of INDEX trial</td>
</tr>
<tr>
<td>Sibutramine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jones et al. (65)</td>
<td>1</td>
<td>10</td>
<td>161/163</td>
<td>−6.2/−2.2</td>
<td>−7.1/−2.5</td>
<td>Weight maintenance after 4 weeks of VLCD treatment</td>
</tr>
<tr>
<td>Apfelbaum et al. (66)</td>
<td>1</td>
<td>10</td>
<td>82/78</td>
<td>−5.2/0.5</td>
<td>−5.4/0.5</td>
<td>Maintenance phase: dose could be increased up to 20mg/day; % weight loss calculated from overall start weight; Diet: 600 kcal/day deficit</td>
</tr>
<tr>
<td>James et al. (68)</td>
<td>2</td>
<td>10</td>
<td>206/57</td>
<td>−10.2/−4.7</td>
<td>−9.6/−4.6</td>
<td></td>
</tr>
<tr>
<td>Orlistat</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>James et al. (102)</td>
<td>1</td>
<td>360</td>
<td>23/23</td>
<td>−8.4/−2.6</td>
<td>−8.4/−2.6</td>
<td>Diet: 600 kcal/day deficit</td>
</tr>
<tr>
<td>Finer et al. (103)</td>
<td>1</td>
<td>360</td>
<td>108/110</td>
<td>−8.3/−5.3</td>
<td>−8.5/−5.4</td>
<td>Diet: 600 kcal/day deficit</td>
</tr>
<tr>
<td>Sjöström et al. (64)</td>
<td>1</td>
<td>360</td>
<td>343/340</td>
<td>−10.3/−6.1</td>
<td>−10.2/−6.1</td>
<td>Weight reduction phase; Diet: 600 kcal/day deficit</td>
</tr>
<tr>
<td>Hollander et al. (90)</td>
<td>1</td>
<td>360</td>
<td>162/159</td>
<td>−6.2/−4.3</td>
<td>−6.2/−4.3</td>
<td>Type 2 diabetics. Diet: 500 kcal/day deficit</td>
</tr>
<tr>
<td>Davidson et al. (91)</td>
<td>1</td>
<td>360</td>
<td>657/223</td>
<td>−8.8/−5.8</td>
<td>−8.7/−5.8</td>
<td>Weight reduction phase; 600 kcal/day deficit</td>
</tr>
<tr>
<td>Hill et al. (97)</td>
<td>1</td>
<td>90</td>
<td>187/188</td>
<td>−5.1/−5.9</td>
<td>−5.9/−6.4</td>
<td>Weight maintenance (eucaloric diet) after 6 months of conventional dieting (1000 kcal/day deficit)</td>
</tr>
<tr>
<td>Rössner S et al. (98)</td>
<td>2</td>
<td>180</td>
<td>239/237</td>
<td>−8.5/−6.4</td>
<td>−8.6/−6.6</td>
<td>Diet: 1st year 600 kcal/day deficit; 2nd year weight maintenance diet</td>
</tr>
<tr>
<td></td>
<td></td>
<td>360</td>
<td>242/237</td>
<td>−9.4/−6.4</td>
<td>−9.7/−6.6</td>
<td></td>
</tr>
</tbody>
</table>
Toubro and Astrup (27). After a marked weight loss in obese patients using traditional energy restriction supported by an anorectic/thermogenic compound, the subjects entered a 1-year weight maintenance programme and were randomized to careful instruction in either calorie counting with a fixed energy intake, or to an ad libitum low-fat high-carbohydrate diet. Both groups were seen as outpatients and had regular reinforced advice during booster sessions. At the end of the programme 1 year later, patients were seen for follow-up. It is clear that even in the hands of a specialized team, a considerable number of patients could not maintain their weight loss. These results show that continuous pharmacological treatment should be considered in patients who have lost weight, but are unable to maintain this reduced weight in the long term. Efficient pharmacotherapy should be considered for weight maintenance purposes as recently shown in a number of clinical trials (66, 68, 97, 98).

Very low calorie diets (VLCDs) are often used to achieve a rapid and substantial weight loss. However, long-term maintenance of this weight loss has been shown to be difficult (104). Pharmacotherapy could be useful to maintain or even improve the initial weight loss with VLCDs. Finer et al. (105) evaluated the efficacy of dexfenfluramine treatment for 6 months in obese patients who had lost weight by means of VLCDs. Patients continued on a hypocaloric diet and either placebo or 15 mg dexfenfluramine twice daily. Patients treated with dexfenfluramine lost an additional 5.8 kg to the weight lost during VLCD; placebo-treated patients, however, regained 2.9 kg of the weight lost during VLCD. The recent study by Apfelbaum et al. (66) showed similar results for treatment with sibutramine after VLCD: the sibutramine-treated group lost an additional 5.2 kg compared to a weight gain of 0.5 kg in the placebo treated group.

The STORM trial (68) showed the effects of sibutramine on weight maintenance after an initial weight loss period with sibutramine 10 mg and a hypocaloric diet calculated from measured basal metabolic rate. In a study by Hill et al. (97), a 24-week period of a hypoeenergetic diet, calculated from estimated energy expenditure, was followed by 1-year treatment with orlistat 30 mg tid, 60 mg tid or 120 mg tid or placebo treatment. After 1 year, subjects treated with 120 mg orlistat regained less weight than placebo-treated patients (32.8% versus 58.7%). Another recent 2-year trial (98) studying the effect of orlistat 60 or 120 mg on weight loss and weight maintenance demonstrated that, after an initial weight loss phase with orlistat (60 or 120 mg tid) combined with a hypocaloric diet, orlistat 60 or 120 mg tid combined with a weight maintenance diet was associated with less weight regain compared to placebo.

EFFECTS OF PHARMACOLOGICAL TREATMENT ON ABDOMINAL FAT DISTRIBUTION

Numerous studies have shown that the health risk associated with obesity is more closely related to visceral fat (3) than to a more peripheral fat distribution. Weight loss, independent of the therapy used, is associated with loss of visceral fat (106). As stated in Table 31.2 the ideal anti-obesity drug preferentially reduces abdominal fat mass.

Visser et al. (107) investigated the effect of fluoxetine on visceral fat reduction, but could not demonstrate any significant effect. In a study by Marks et al. (108) treatment with dexfenfluramine in obese type 2 diabetic subjects resulted in a selective reduction of visceral fat area, measured by magnetic resonance imaging. Meta-analysis of four long-term studies with sibutramine showed a significantly greater decrease in waist circumference, as an indicator of visceral fat mass, in sibutramine-treated subjects compared with those receiving placebo (53). The same paper reported on the preliminary data on absolute changes in visceral fat, measured by computed tomography (CT) scan, after 6 months of treatment with sibutramine, as part of the STORM trial. In these patients visceral fat decreased by 22%, which was associated with significant decreases in associated risk factors such as fasting glucose and insulin and serum triglycerides. Reduction in blood pressure was most significant in subjects with the largest visceral fat reduction (53). However, studies comparing the effect of caloric restriction with that of pharmacotherapy without caloric restriction are needed to determine the role of pharmacotherapy in reducing visceral fat (106).

FUTURE PROSPECTS WITH PROMISING MOLECULES

Recent years have been very exciting for researchers
working in the field of obesity. The discovery of the \textit{ob} gene and its product leptin (109) has stimulated research in the field of genetics and molecular biology, with rapid advances being made in the understanding of weight-regulating mechanisms. This has led to the identification of a series of potential new targets for the treatment of obesity. However, experience has shown that it is not easy to translate this knowledge into clinically safe and effective pharmacological compounds. An important reason is that results found in laboratory animals are not always reproducible in human subjects. We will focus on a few of these newly identified targets and the corresponding compounds in development, which can be divided into those acting on energy intake and those acting on energy expenditure (110).

\textbf{Drugs Altering Energy Intake}

Appetite and food intake are modulated by several hormones and neurotransmitters acting in a complex interaction. Two major systems can be identified: the short-term regulation of food intake with cholecystokinin (CCK) and glucagon-like-peptide 1 (GLP-1) as major representatives and the long-term regulation of food intake through the leptin system. Recent data seem to suggest an interaction between these two weight-regulating systems (111–113).

\textbf{Cholecystokinin and Glucagon-like Peptide 1}

Cholecystokinin and GLP-1 are both gastrointestinal hormones secreted by the duodenum in the presence of food. Cholecystokinin inhibits gastric emptying, contracts the pyloric sphincter and stimulates gallbladder contraction and pancreatic exocrine secretion (114). Intravenous infusion of cholecystokinin or GLP-1 has a satiety effect in both lean (115,116) and obese subjects (115,117). The satiety effect of cholecystokinin is mediated through its type A receptor found in the periphery and the central nervous system (118). Cholecystokinin agonists could be useful in the treatment of obesity but should be orally active, selective for the CCK-A receptor and should have a long biological half-life (119).

Glucagon-like peptide is an incretin hormone, stimulating the pancreatic secretion of insulin after food intake (120). In this context, GLP-1 has been extensively studied as an anti-diabetic agent and could be particularly useful for the obese type 2 diabetic patient through its action on both hyperglycaemia and food intake (121). However, GLP-1 is metabolized very quickly by the dipeptidyl-peptidase IV (DPP-IV) enzyme (122), making it difficult to turn GLP-1 into a clinical useful therapeutic agent. Recently, considerable effort has been put into the development of DPP-IV resistant analogues of GLP-1 (123), DPP-IV inhibitors (124) and GLP-1 receptor agonists such as exendin-4 (125).

\textbf{The Leptin System}

Since the discovery of leptin in 1994 (109), extensive research has shown that is more than just a simple mediator of energy intake and expenditure and that it plays a role in different physiological processes such as reproduction and insulin secretion (126).

Leptin was first discovered through the \textit{ob}/\textit{ob} mouse, where due to a mutation in the \textit{ob} gene, no leptin is secreted (109). In these animals, treatment with leptin resulted in reduction of body weight (109). Obese humans, however, appear to have elevated leptin levels correlating with the amount of body fat (127). In a few cases mutations in the obese gene (128,129) or the leptin receptor gene (130) have been described. Treatment of a 9-year-old girl with a congenital leptin deficiency with recombinant leptin resulted in an important reduction of body weight, predominantly body fat (131).

The use of leptin as an anti-obesity agent is limited by the fact that it has to be given subcutaneously and in very high doses, which could result in inflammatory reactions at the injection site. More promising perspectives will probably come from leptin analogues and leptin receptor agonists.

Leptin exerts its action through different neurotransmitters such as neuropeptide Y (NPY), glucagon-like peptide 1 (GLP-1), \textit{\&}-melanocyte-stimulating hormone (\textit{\&}-MSH), corticotrophin-releasing hormone (CRH) and cocaine and amphetamine regulated transcript (132,133). Extensive research has been done on the role of these peptides in the regulation of food intake in both animals and humans.

Two major pathways of post-receptor leptin signalling effects can be described: the NPY pathway leading to a decrease in food intake and the proopiomelanocortin pathway with an opposite effect.
NPY is one of the most potent stimulators of food intake (134) and six different receptor subtypes have been cloned. The type 1 and type 5 receptors appear to be most important receptors in the regulation of food intake (135,136). Several NPY receptor antagonists are now in different stages of preclinical and clinical development.

Melanocortins are peptides cleaved from its precursor pro-opiomelanocortin, with α-MSH being the most important melanocortin in the regulation of food intake (137). It binds to the melanocortin receptors MC3-R and MC4-R, resulting in a decrease in food intake (138). The agouti-related protein (AGRP) selectively antagonises MC3-R and MC4-R (139). Recently, melanin-concentrating hormone (MCH) was identified as another functional antagonist of α-MSH acting on a separate G-protein-coupled receptor, somatostatin-like receptor 1 SLC-1 (140).

The most recently discovered families of hypothalamic peptides involved in the regulation of food intake are the cocaine and amphetamine regulated transcript peptides (CART) (141) and the orexins (142) or hypocretins (143), confirming the complex neuroendocrine system of weight regulation.

**Drugs Altering Energy Expenditure**

**The β3-Adrenergic Receptor**

The β3 adrenergic receptor, first discovered in the early 1980s (144), is mainly located in adipose tissue and plays an important role in adrenergic stimulation of lipolysis and thermogenesis in white and brown adipose tissue. Several pharmaceutical companies have developed β3-agonists. Early compounds yielded positive results in animals but showed rather disappointing results in humans (145,146), which could in part be explained by the substantial differences between the animal and human receptor (144,147). After the cloning of the human receptor in 1989 (148), new highly selective compounds were developed (147). However, the effectiveness of β3-adrenergic receptor agonists remains questionable since the amount of brown adipose tissue in humans is very small (147).

**Uncoupling Proteins**

Uncoupling proteins (UCPs) are mitochondrial proteins that uncouple adenosine triphosphate (ATP) production from mitochondrial respiration, producing heat leading to a net increase in energy utilization (149). UCP1 was identified in the 1980s and is mainly located in brown adipose tissue (150). Recently two new uncoupling proteins were identified: UCP2 is widely expressed in human tissues (151) and UCP3 (152) is found predominantly in skeletal muscle. Many papers have focused on the expression of UCP1 (153–155), UCP2 (156) and UCP3 (157) in obesity and type 2 diabetes, yielding conflicting results.

**CONCLUSION**

Despite the extensive research performed with dexfenfluramine, this drug was withdrawn from the market because of its association with cardiac valvulopathy. New drugs such as sibutramine and orlistat are replacing dexfenfluramine.

Both sibutramine and orlistat have been shown to be efficacious, with a mean weight loss of approximately 10% of baseline body weight. This is in line with recent recommendations that a modest weight reduction up to 10% has important beneficial health effects. In clinical trials, however, the net benefit above placebo results seems less spectacular. However, it should be kept in mind that these results have been obtained under strictly controlled conditions, also for the placebo groups. The future will show whether these effects will be as positive and as long-lasting in daily life conditions.

It is important to acknowledge that on an individual basis the clinician’s decision to treat an obese patient with weight loss medication may be a reasonable one, despite the uncertainties about the long-term benefits of pharmacotherapy in the population. We learned that from the dexfenfluramine experience. For some obese patients, who respond well to these drugs and can tolerate the adverse effects, pharmacotherapy is undoubtedly beneficial, as stated recently by Williamson in an editorial comment (158).

The benefit risk ratio of the new anti-obesity drugs is not yet possible to determine because of the lack of long-term evaluation of their safety. Obesity is now recognized as a serious health problem and given the lack of long-term success of non-surgical and non-pharmacological treatments for obesity,
there is clearly a need for efficient weight-reducing drugs (159). Since 10% weight loss may not be enough for seriously obese subjects, the search is on for even more effective compounds. The development of such new compounds, acting on different mechanisms, is urgently required: they include leptin analogues, NPY antagonists, orexins, glucagon-like peptide and other promising compounds.

REFERENCES


59. Martin KF, Needham PL, Atkinson J, Cowan A, Heal DJ, Bucket WR. Rat striatal and mesolimbic D1 receptor binding is not altered by antidepressant treatments including ECS and sibutramine HCL (Abstract). Br J Pharmacol 1988; 95: 896P.


65. Jones SP, Smith IG, Kelly F, Gray JA. Long-term weight


95. Johansson G, Marin P, Lönn L, Ottosson M, Stenlöf K, Björntorp P, Sjöström L, Bengtsson B. Growth hormone treatment of abdominally obese men, reduces abdominal fat mass, improves glucose and lipoprotein metabolism and


138. Schioth HB, Mucenie R, Larsson M, Wikberg JE. The melanocortin 1,3,4 or 5 receptors do not have binding epitope for ACTH beyond the sequence of alpha-MSH. J Endocrinol 1997; 155: 73–78.


