

GET TO GRIPS WITH OBESITY

(3) PHARMACOTHERAPY

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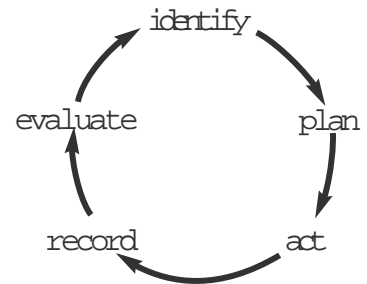
Obesity has a substantial human cost as well as serious financial consequences for the National Health Service. For some patients, diet and exercise do not make enough impact on their condition. This article looks at the treatment of obesity using drugs



identify gaps in your knowledge

1. Should patients taking orlistat take multivitamins?
2. Can you list three counselling points for a patient dispensed sibutramine for the first time?
3. What factors influence how long orlistat or sibutramine can be used for?

This article relates to the Royal Pharmaceutical Society's core competency of "common disease states and their drug therapies" (see "Medicines, ethics and practice — a guide for pharmacists", number 25, July 2001, p104). You should consider how it will be of value to your practice.



Resorting to the use of drugs to tackle obesity by no means represents the ideal scenario, but many patients who choose to make lifestyle changes to combat their weight problems either fail to maintain their commitment to change, or fail to lose an adequate amount of weight. It is in this situation that pharmacists are most likely to excel. Obesity should be regarded as a chronic disease rather than a lifestyle choice resulting from overeating and lack of exercise. At present, there are three methods by which drugs aim to achieve weight loss: increasing energy expenditure, decreasing food intake (appetite suppressants) and reducing absorption.

Despite the high incidence of obesity, we currently have little choice in anti-obesity drugs. Sympathomimetics (eg, ephedrine) are thought to increase energy expenditure by stimulating lipolysis and thermogenesis, but clinical trials have shown little benefit in humans and serious side effects (eg, hypertension and tachycardia) are well known. Thyroxine will also increase energy expenditure, but it is associated with loss of lean tissue and should only be used in patients with proven hypothyroidism.

The "appetite system" has many components. In the brain, the catecholamine (eg, noradrenaline) and serotonin pathways are involved. Although many drugs are capable of suppressing appetite, few are licensed because of dangerous adverse effects. Furthermore, simply suppressing appetite does not encourage healthy eating habits. Fenfluramine and dexfenfluramine, which are classed as serotonin-releasing agents, were withdrawn in 1997 after reports of valvular heart disease and pulmonary hypertension. This was followed by the withdrawal of phentermine and diethylpropion (which alter catecholamine levels) in 2000, leaving a void in drug therapy for obesity. The void was filled by the launch of orlistat (Xenical) in 1998 and sibutramine (Reductil) in 2001 and these are the two drugs currently recommended to treat obesity in the United Kingdom.

Bulk-forming agents such as methylcellulose are also available (they aim to make the patient feel full), but there is little evidence of efficacy. Orlistat and sibutramine should only be used for people at medical risk due to obesity (not for cosmetic reasons). The use of both drugs concomitantly is not technically unlicensed and given their different mechanisms of action, there might be some benefit from combining these drugs in the future. However, there is limited

data on combination therapy and existing data shows this to be no more effective than the use of either drug alone. Therefore until we have further information, the two should not be used together.

CLINICAL EFFECTIVENESS

The National Institute for Clinical Excellence has issued guidance on the use of both drugs. NICE looked at 14 trials of orlistat and concluded that the drug is clinically effective in reducing weight by a mean of 2–5kg over placebo per year. Weight loss was accompanied by significant reductions in total cholesterol and blood pressure.

For sibutramine, NICE looked at 16 trials and concluded that sibutramine produced a mean, dose-dependent weight loss of 4–5kg over placebo at one year. People who had lost weight by taking sibutramine were more likely to maintain the loss if the treatment period was extended compared with those who were randomised to a diet and exercise programme. Risk factors for cardiovascular morbidity (eg, cholesterol levels) decreased but not all to a significant degree. Improvement in blood glucose control was seen in patients with type 2 diabetes, but not all improvements were significant.

ELIGIBILITY FOR DRUG THERAPY AND WHICH DRUG TO USE

The initial eligibility criteria require three questions to be asked:

1. **Does the patient have a body mass index (BMI) over 30, or a BMI over 28 (27 for sibutramine) and one obesity related condition (eg, type 2 diabetes, hypertension, hypercholesterolaemia)?** If the answer is yes, the patient meets both licensing and NICE criteria for being considered for drug therapy.
1. **How much weight has the patient managed to lose recently?** The gateway to drug therapy depends on the medicine to be prescribed. To be prescribed orlistat, a patient must have successfully lost 2.5kg through lifestyle measures (ie, diet, exercise and behavioural change) within one month of receiving his or her first prescription. Conversely for sibutramine, only patients who have been unable to lose and maintain at least 5 per cent of their total body weight within three months (despite a proper attempt at weight loss) should receive a prescription. The orlistat approach stems from the opinion that only patients who are "serious" about weight loss should be entitled to drug treatment (the manufacturer maintains that these are the patients that benefit optimally in the long term) but arguably, it is individuals

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who fail to lose weight who really need the extra help. This seems to be the sibutramine approach.

- 1 **How old is the patient?** Both drugs have age restrictions because of the lack of safety and efficacy data for certain age groups.

Clinical parameters such as side effects, cautions, contraindications and interactions will further influence whether orlistat or sibutramine is selected for a patient and the two drugs should be compared. What is clear and well accepted within the field of obesity management is the requirement for pharmacotherapy to be integrated with advice, support, diet, physical activity and behavioural strategies. Panel 1 gives a summary of the comparison between the two drugs.

ORLISTAT

Orlistat promotes weight loss by reducing the absorption of energy dense fat. The drug is a potent inhibitor of pancreatic and gastric lipases, which are enzymes responsible for breaking down dietary fat so that it can be absorbed. Covalent binding of the drug to these enzymes results in long-lasting inhibition and up to 30 per cent of dietary fat is able to pass through the gastrointestinal tract unabsorbed.

There are few restrictions to using orlistat, most being due to the lack of evidence of use in certain patient groups (eg, pregnancy, breastfeeding). And because the drug is not absorbed to a significant extent, systemic side effects are rare. However, once prescribed, patients may choose not to continue with therapy because of gastrointestinal effects (eg, oily spotting from the rectum, flatus with discharge and faecal urgency). Some patients learn which food types result in these side effects, and change their eating habits (avoidance behaviour) so that with time, drug therapy drives a healthier diet, ie, orlistat has a second possible mode of action.

Salient points to consider when dispensing orlistat are:

- 1 One capsule should be taken before or up to one hour after main meals, up to three times a day. Doses can be omitted if a meal is missed or is fat free.
- 1 Dietary advice is required. Orlistat should be used in conjunction with a diet which is slightly low in calories and contains no more than 25–30 per cent fat. The daily intake of macronutrients should be divided over the three main meals and snacking on fatty food (eg, crisps and chocolate) between meals, should be avoided. This is an opportunity to encourage healthy eating habits.
- 1 Gastrointestinal side effects can be distressing if patients are not forewarned, but if the pharmacist is able to explain why they occur, patients are more likely to continue with therapy. Fur-

Xenical and Reductil are the two anti-obesity drugs currently available in the UK

thermore, gastrointestinal changes indicate that the drug is working and side effects should decrease with use.

- 1 It has been found that some patients choose not to take orlistat with meals that are likely to cause the worst side effects (eg, when “dining out”) but do take a capsule when they eat less fatty foods. This defeats the object and should be discussed with the patient.
- 1 The summary of product characteristics warns that malabsorption of fat soluble vitamins (A, D, E and K) may occur. Although there have been few cases of vitamin deficiency, patients may wish to take a multivitamin supplement and if so, should be advised to take the supplement at least two hours after taking orlistat. Because long-term use of orlistat might reduce vitamin K absorption, theoretically this could interact with anticoagulant therapy. The manufacturer recommends that international normalised ratio (INR) values should be monitored in patients stabilised on warfarin but regular monitoring of these patients takes place in any case.

SIBUTRAMINE

Sibutramine inhibits the reuptake of both serotonin and noradrenaline (this is different from fenfluramine, etc) and this means that it has two modes of action. Firstly, sibutramine acts centrally leading to a sensation of fullness (satiety) and there have been reports of a 20 per cent reduction in food intake (eg, leaving food on the plate). Secondly, sympathetically mediated thermogenesis maintains “original” basal metabolic rate (BMR) even when weight loss occurs. Normally, BMR will decrease as weight is lost, thus conserving

PANEL 1: COMPARISON OF ORLISTAT AND SIBUTRAMINE USE

	Orlistat	Sibutramine
Eligibility for treatment	<ol style="list-style-type: none"> 1 BMI over 30 or over 28 plus at least one co-morbidity 1 Display weight loss of at least 2.5kg through lifestyle changes within the last month 1 Aged between 18 and 75 years 	<ol style="list-style-type: none"> 1 BMI over 30 or over 27 plus at least one co-morbidity 1 Unable to display and maintain a weight loss of at least 5% through lifestyle changes within three months 1 Aged between 18 and 65 years
Continuation of therapy	Therapy can be continued if there is a 5% weight loss at 3 months and a 10% (cumulative) loss at 6 months	Therapy can be continued if the patient loses 2kg in the first four weeks and 5% of their weight (at the start of therapy) in the first three months
Maximum duration of therapy	2 years	1 year
Contraindications, cautions, side effects	Few	Many (plus special requirement to monitor blood pressure)
Current cost of one year’s treatment	£537 (based on one capsule three times a day)	£456 (10mg daily) or £510 (15mg daily)

action : practice points

1. Speak to a patient taking orlistat or sibutramine and find out what support they have received from primary care staff (including dietitians). Does he or she have a clear treatment plan? What kind of side effects have been experienced?
2. According to NICE, local "obesity action plans" that formulate ways of targeting key groups and offering systematic weight management services should be set up. Find out if such plans exist in your community and write down how you could contribute them.
3. Reinforce the benefits of weight loss to patients by offering regular cholesterol or blood glucose tests.

evaluate

How could your learning have been more effective?
What will you do now and how will this be achieved?

energy and making it hard to lose more weight. A maintained BMR means that enough calories are still "burnt" to result in an energy balance conducive to weight loss.

Because sibutramine is well absorbed and affects both sympathetic and central nervous systems, it has many more contraindications, cautions, side effects and interactions compared with orlistat, ie, sibutramine is suitable for fewer patients. Examples of contraindications due to central effects are psychiatric illness or a history of major eating disorders. Sibutramine should not be used concomitantly with most antidepressants or antipsychotics. Examples of contraindications due to sympathetic effects are glaucoma, a history of coronary artery disease, congestive heart failure, stroke or cardiac arrhythmias. Like orlistat, sibutramine is contraindicated in hypersensitivity, pregnancy and breastfeeding.

Because centrally-acting drugs have the potential to impair the performance of skilled tasks (eg, driving), the manufacturer of Reductil warns about this. However, the drug did not affect psychomotor or cognitive performance of volunteers in trials.

There is a special requirement for monitoring blood pressure in every patient prescribed sibutramine. Both blood pressure and pulse rate should be checked every two weeks for the first three months, every four weeks for the second three months, and then at least every three months after that. If an increase in heart rate of 10bpm or a rise in blood pressure of at least 10mmHg (systolic or diastolic) is found at two consecutive checks, therapy should be stopped. Therapy should also be stopped if blood pressure exceeds 145/90mmHg in patients whose hypertension was previously controlled. Any patients reporting breathing problems, chest pain, swollen ankles, a racing pulse or palpitations should be investigated urgently.

In spite of this special requirement, the majority of patients on sibutramine do not show significant increases in blood pressure and the drug is only contraindicated in uncontrolled hypertension. The STORM trial (605 patients enrolled in a weight loss and maintenance programme) revealed an average increase in blood pressure in the range of 0.5mmHg systolic and 2.3 mmHg diastolic,¹ and the number of patients suffering adverse effects was small. Moreover in practice, most patients experience a fall in blood pressure as weight loss occurs. Most side effects (eg, dry mouth and insomnia) occur during the first four weeks but severity usually decreases with time. It is usually patients who do not respond adequately to sibutramine (see below) who are more likely to experience side effects.

Points to consider when dispensing sibutramine are:

1. One capsule should be taken in the morning with or without food, but with a glass of water. If a dose is missed, the patient should not double the next dose, but should continue as before.
1. Again, dispensing is an opportunity to support a long-lasting change in lifestyle. The idea of not eating everything on your plate is worth emphasising. Bear in mind that instilling healthy eating and activity habits will help to prevent weight regain when therapy is inevitably stopped.

1. Do not create unnecessary anxiety regarding blood pressure monitoring. This is an area for reassurance and perhaps even health promotion.
1. Patients should be cautioned about the use of over-the-counter decongestants because they can increase the likelihood of raised blood pressure.

COST EFFECTIVENESS AND DURATION OF THERAPY

To attain adequate cost effectiveness for the use of orlistat, patients need to lose at least 5 per cent of their total body weight (measured at the start of drug therapy) within the first three months and at least 10 per cent within the first six months. NICE recommends that prescribing beyond these periods should only continue if these targets are met. Although Xenical's license allows it to be used for a maximum of two years, there is no evidence of efficacy with therapy continued over 12 months and NICE recommends that treatment should not normally continue for more than a year. Published safety data do not extend beyond two years but a diabetes study due to be reported within the next year will probably extend the licensed duration of therapy to four years.

For cost-effective prescribing of sibutramine, the starting dose should be 10mg daily and continuing therapy beyond four weeks must be supported by a weight loss of 2kg. Continuing therapy beyond three months requires a 5 per cent reduction in total body weight measured at the start of treatment. The dose of sibutramine can be increased to 15mg daily in patients who have not responded adequately (ie, fail to lose 2kg within the first four weeks), but therapy must be stopped if a 2kg loss within four weeks at the higher dose is not achieved.

THE FUTURE

Both orlistat and sibutramine are still "black triangle" drugs and any suspected adverse reaction should be reported via the yellow card system. Recently, Italy suspended its marketing authorisation for sibutramine products but after reviewing UK data, the Medicines Control Agency has stated that the current situation regarding sibutramine is satisfactory. NICE has recognised a need for further research on both drugs, particularly in light of the lack of experience of long-term use. Suggested investigations include the rate of weight regain after treatment is stopped and whether therapy can be recommenced, the clinical benefits of short term weight loss compared to long term weight loss, the safety and efficacy of use in older and younger populations and whether gender, ethnic group or family history affects efficacy. Reviews of the NICE guidance are scheduled for 2004.

As research improves our understanding of obesity, our choice of treatments should widen. New substances thought to be associated with appetite control have been discovered. Peptides such as enterostatin have been linked to reducing fat intake and antagonists to receptors for neuropeptide-Y (which increases appetite) are being studied. Work is being done on the hormone leptin (produced by an obesity gene and secreted from fat cells) and its receptors, and recently, a protein that may influence energy expenditure in various tissues (UCP2) has been identified.

CONCLUSION

The car, television, computer games, the whole way in which we live today plague those who are trying to lose weight. But until we live in a less obesity inducive environment, or until a cure is found, we need to ensure that obesity management is not put on hold. Although drugs cannot replace exercise or dieting and should not be used alone, drug therapy is appropriate as long as it is done in accordance with current recommendations and with coordinated support for the patient. This is where pharmacists can contribute most.

REFERENCES

1. James WP, Astrup A, Finer N, Hilsted J, Kopelman P, Rossner S et al. Effect of sibutramine on weight maintenance after weight loss: a randomised trial. STORM study group. *Lancet* 2000;356:2119-25.