Treatment: Drug Therapy

Drug management has an important role to play in primary care, both as a treatment for obesity in its own right and as a prevention for diabetes, coronary heart disease (CHD) and premature death.

The principal concerns when considering drug treatments for obesity management are:

- Whether it is clinically appropriate to progress to pharmacotherapy
- The suitability of the patient for drug treatment
- The safety profile of the drug
- The efficacy of the drug

Drug therapy should be viewed as an adjunct to lifestyle change, therefore, adequate provision for continual monitoring and support should be in place as part of an overall weight management programme. Drugs expand the opportunities for treating obesity, but, in order to maximise this they need to be used in an appropriate and responsible manner. Prescribing a weight loss drug for a particular patient will always be an individual decision that should be reached in partnership with the patient.[1] The suggestion of using drug treatment may be made by the doctor or requests may come directly from the patient.

When prescribing anti-obesity medication, the doctor needs to:

- Ensure lifestyle changes have been implemented
- Abide by the prescribing guidelines
- Provide information on the mechanisms of action and the side effects of the drug
- Discuss their own and the patient's expectations from the drug treatment
- Provide information about the 'rules' governing the continuation of drug treatment
- Ensure the appropriate level of support can be offered alongside the drug treatment

When requesting anti-obesity medication, the patient needs to:

- Ensure that they are well informed about the drug: its potential for weight loss, the side effects and the conditions of use
- Accept that lifestyle changes need to accompany drug therapy
- Set realistic goals for what they want to achieve with drug treatment

Suitability of individual patients for treatment with drugs is a clinical judgement. To avoid disappointment, it is valuable to invest time in discussing the merits and drawbacks of the treatments, especially in relation to the need to combine the drugs with lifestyle changes. When used appropriately, drugs offer an additional level of support to the patient attempting to control their weight.

Current anti-obesity medication

Two drugs currently licensed for the treatment of obesity are sibutramine (Reductil) and orlistat (Xenical). Compared with older and withdrawn drugs, these medications have been much more vigorously evaluated. The National Institute for Clinical Excellence (NICE) has issued guidelines on the use of both medications. The drugs should be used as a means of reducing health risk in those with a BMI of ≥30 kg/m^2 . NICE guidance is also given on the use of drugs at a lower BMI (27–30kg/m^2) when obesity-related co-morbidities are present.

Sibutramine

Mode of action

Sibutramine acts by inhibiting the re-uptake of the neurotransmitters noradrenaline and serotonin from receptor sites in the hypothalamus. This results in a dual centrally acting mechanism which aids weight loss:

1. Enhanced satiety: The increased availability of these neurotransmitters enhances satiety (via serotonin stimulation of the 5HT2A & 2C receptors). Therefore, smaller quantities of food will lead to a feeling of fullness. Unlike the use of appetite suppressants (aimed at reducing hunger), patients on sibutramine experience a greater degree of satiety and consequently eat less with each meal. In other words they enhance the signal to stop eating, whereas appetite suppressants reduce the signal to start eating.

2. Attenuating the decline in basal metabolic rate (BMR): Sibutramine is also thought to attenuate the decline in BMR by activating the sympathetic nervous system centrally. This effect is beneficial because sibutramine prevents the BMR from falling as weight is lost (a well known phenomenon which makes it harder to subsequently lose more weight). The side effects of sibutramine (increased heart rate and increased blood pressure) are also due to this 'sympathetic' activity. Sibutramine was originally developed as an antidepressant, but in clinical trials was found to have weight loss effects. Sibutramine does not have any addictive or anti-depressant properties.[2]

Using the drug

The starting dose of sibutramine is 10 mg/day, with the potential to increase to a maximum of 15 mg/day after four weeks in line with the sibutramine summary of product characteristics (SmPC). Patients taking sibutramine are encouraged to take advantage of a comprehensive lifestyle pack - the Change For Life Programme. This is a step-by-step behavioural programme, which includes food and activity diaries, as well as advice on diet and physical activity changes. Healthcare professionals can request copies of the Change For Life Programme by contacting Abbott Laboratories on 01628 644392.

Side effects

The most commonly reported side effects include dry mouth, insomnia, anxiety and constipation. During the STORM (Sibutramine Trial of Obesity Reduction and Maintenance) trial, at a 10 mg dose of sibutramine, 1% of patients had to be withdrawn because of increases in blood pressure; with 15 mg doses, a further 2% were withdrawn.[3] Patients taking the drug should have their blood pressure monitored fortnightly for the first 3 months, then monthly for the next 3 months and quarterly thereafter.

Withdraw the drug if:

- Blood pressure is above 145/90 mmHg on two occasions
- Blood pressure rises by 10 mmHg from baseline
- Pulse rate rises by 10 bpm from baseline
- Arrhythmias occur

Clinical trials show the average rise in diastolic pressure to be < 4 mmHg and improvements in blood pressure have been observed in patients who lose weight with the drug.[4,5]

Drug efficacy

A large number of studies have been published, but the most prominent data on the efficacy of sibutramine comes form the STORM Study Group.[3] In this two-year study, all patients were prescribed sibutramine (10 mg daily) and provided with advice on diet and physical activity for the first six months of the trial. Those successful at losing at least 5% of their starting body weight (77% of the study group) then entered a second phase where they were randomised to differing doses of sibutramine (15-20 mg per day) or placebo. At 24 months, mean weight loss for the sibutramine group was 8.9 kg compared with 4.9 kg in the placebo group. In addition to weight loss, there were significant improvements in blood lipids (predominantly triglycerides and HDL cholesterol) and measures of insulin resistance. Treatment with sibutramine has also been shown to benefit patients with diabetes.[6]

Trials where sibutramine has been combined with another treatment strategy are also of interest, for example with a very low calorie diet (VLCD). In one study, patients who lost

at least 6 kg following a 4-week VLCD programme were randomised to 12 months treatment with sibutramine or placebo.[7] Those randomised to sibutramine continued to lose, on average, another 5.2 kg, compared with the placebo group who gained on average 0.5 kg.

Contraindications

Sibutramine is contraindicated with:

- Ischaemic heart disease and cardiac failure
- Arrhythmias or cerebrovascular disease
- Uncontrolled hypertension
- Concomitant or recent use of monoamine oxidase inhibitors, other centrally-acting drugs or tryptophan
- Concomitant use of other centrally acting anorectic drugs

The drug should not be used during pregnancy and during lactation and it is not licensed for use in children.

NICE guidance

- Sibutramine should be prescribed only in adults aged 18–65 years who have a BMI of ≥30 kg/m^2 or a BMI of ≥27 kg/m^2 in the presence of significant co-morbidities
- Eligible patients are expected to have previously made serious attempts to lose weight by lifestyle modification alone
- Continuation of therapy beyond four weeks should be supported by evidence of a 2 kg weight loss, and beyond three months by evidence of at least 5% of initial body weight
- Sibutramine should be stopped if patients do not lose weight as described above
- There should be concomitant advice, support and counselling on diet, physical activity and behavioural strategies from appropriate health professionals
- Sibutramine should not be prescribed unless adequate arrangements for monitoring both weight loss and adverse effects can be made
- People who are prescribed sibutramine should have their blood pressure checked regularly

NICE also advise that treatment is not currently recommended beyond the licensed indication of 12 months. They recommend that the longer-term effects of the drug be addressed by further research.

Orlistat

Mode of action

Orlistat is a potent inhibitor of the enzyme pancreatic lipase. Acting in the lumen of the gastrointestinal tract, the drug inhibits the breakdown of dietary triglycerides into free fatty acids and glycerol molecules. As a result, up to 30% of dietary fat passes unabsorbed through the gastrointestinal tract compared with the normal 4% faecal fat content.[8] The second therapeutic factor attributed to the drug is the learned aversion to high fat foods as a result of experiencing gastrointestinal treatment effects. In other words, patients taking the drug have an implicit reason to reduce their intake of dietary fat.

Using the drug

The therapeutic dose of the drug is 120 mg, taken three times daily, i.e. with each main meal. If a dosage is missed, the drug can be taken up to one hour after a meal, and if a meal is missed altogether the drug should be omitted for that occasion. To avoid or minimise the gastrointestinal side effects, and to encourage important long-term behavioural change, the importance of regular meals and a low fat diet needs to be emphasised. This should be in place before the drug is prescribed. Ideally, a consultation with a dietitian should be arranged to ensure that the combination of diet and drug therapy is maximised. However, if referral to a dietitian is not possible, then other healthcare professionals should be equipped with the appropriate knowledge and skills to advise patients on a diet which contains no more than 30% fat.

Patients taking orlistat are encouraged to take advantage of the patient support line MAP (Motivation, Advice and Pro-active support). Written materials, pedometers and food and activity diaries are provided as well as advice and encouragement on how to change lifestyle. Patients prescribed orlistat or being considered for prescription with the drug can contact the help line number on 0800 731 7138 or visit the website **www.xenicalmap.co.uk** .

Side effects

The most commonly reported side effects relate to the undigested fat – namely loose oily stools, flatulence and spotting – hence the importance of appropriate dietary advice. However, those eating an appropriate healthy diet should not be troubled by these events, as the tendency is for them to occur predominantly at the start of treatment, when the patient may not recognise the fat content of certain foods. In clinical trials of the drug, plasma concentrations of the fat-soluble vitamins A, D, E & K stayed within reference ranges, however some clinicians recommend the use of multivitamins with long-term treatment with orlistat.[9] If multivitamin supplementation is considered appropriate then it should be taken two hours before or after the administration of orlistat, and ideally at bedtime.

Drug efficacy

There have been several large-scale randomised controlled trials evaluating the role of orlistat in obesity treatment. Two large placebo-controlled trials have examined the effect of orlistat in addition to advice to follow a 500–800 kcal deficit diet.[10,11] Similar results have been reported from both. The average weight loss at one year was 6% in the placebo group compared with 10% in the patients prescribed orlistat. Patients who crossed from placebo to orlistat for the final year of the study lost additional weight, compared with patients who crossed to placebo and gained weight. All of the studies conducted have shown that orlistat can achieve reductions in plasma lipid levels and that risk factors such as blood pressure, glycaemia and insulin resistance can be improved in susceptible individuals.[12,13]

The Xendos trial provides information about the longer term (4-year) efficacy of orlistat, as well as its role in the treatment and prevention of type 2 diabetes.[14] The results of the study showed that in orlistat-treated subjects there was an overall risk reduction of 37% in the development of diabetes, compared with those following lifestyle treatment alone.

Contraindications

As less than 1% of the drug is systemically absorbed, the contraindications to drug treatment are not extensive.[15] However, orlistat should not be used in patients with malabsorption or cholestasis. In addition, it should not be used during pregnancy or whilst breastfeeding. It is not licensed for use in children (although it is approved in the US for 12–16-year-olds). Co-administration of orlistat with cyclosporine is not recommended.

NICE guidance

- Orlistat should be prescribed only in adults aged 18–75 years who have a BMI of ≥30 kg/m^2 or a BMI of ≥28 kg/m^2 in the presence of significant co-morbidities
- When treatment with orlistat is offered, arrangements should be made for appropriate health professionals to offer regular advice, support and counselling on diet, physical activity and strategies to manage behaviour
- People should only continue on this treatment beyond 3 months if they have lost at least 5% of body weight from the start of drug treatment

There is now safety and efficacy data on orlistat beyond 2 years and the SmPC for orlistat does not place a restriction on the duration of treatment. However, continuation of therapy would obviously be assessed in relation to the level of weight loss maintenance.

Selecting patients

No comparative studies have yet been published, but with such diverse modes of action and contraindications to treatment, the suitability of patients for each drug treatment will be based on an individual patient profile. Drug treatment is and should remain an adjunct to, rather than a replacement for, lifestyle intervention – additional benefit will always be gained from improving diet and increasing exercise levels. Since there is no cure as such for obesity, weight maintenance strategies need to be in place when drug treatment is discontinued. Using the drugs in combination has not been studied, and is currently contraindicated.

Discuss thoroughly with patients their expectations from drug treatment. All patients should be aware that drug treatment is an adjunct to lifestyle treatment and not a substitute for this. Other patients may be reluctant to use medication based on their fears over the safety of older drug treatments. Care should be taken to explain the process involved in evaluating anti-obesity medication and the guidance provided by NICE and other professional bodies such as the Medicines and Healthcare Products Regulatory Agency.

Points to remember

- Drugs should not be thought of as a stand-alone treatment for obesity
- Drug treatment is an adjunct to, rather than a replacement for, lifestyle intervention
- There is no miracle anti-obesity drug
- Different patients will respond better to different drug treatments
- There is no ‘cure’ for obesity, so weight maintenance needs to be addressed through long-term changes to diet and physical activity

Metformin is frequently prescribed to obese individuals, but its precise role in obesity management is unclear. It brings about improvements in insulin sensitivity, and is therefore useful in the Metabolic Syndrome, and of course has a specific role in type 2 diabetes and PCOS, but whether it has a part to play in obesity management, either alone or in combination with orlistat or sibutramine has yet to be formally evaluated.

Withdrawn and older drug treatments

The following medications are not endorsed by NICE, have not undergone modern clinical evaluation and have no role in the long-term treatment of obesity:

- Duromine (phentermine)
- Ionamin (phentermine)
- Diethylpropion (amfepramone)
- Tenuate Dospan (amfepramone)

In addition the following medications should not be prescribed for obesity treatment per se:

- Diuretics
- Chorionic gonadotrophin
- Amphetamines
- Thyroid hormones (unless the obese patient has biochemically proven hypothyroidism)
- SSRIs

Over-the-counter preparations

Over-the-counter weight loss pills and products are regularly advertised in magazines, alternative health food shops and on the internet. Their appeal is understandable, especially when the advert is accompanied by impressive 'before and after treatment' photographs, not to mention outstanding claims about efficacy. Patients should be made aware of the fact that currently none of these products are backed up by reliable published scientific evidence, and that their long-term safety has not been established.

There are other herbal and alternative medicines that are promoted to consumers that may have a biological rationale for the claimed weight loss properties, for example chitosan and green tea catechins. However, their true efficacy in obesity treatment remains to be properly and fully evaluated. [16,17]

Drugs that can cause weight gain

Several medications can influence weight. The mechanism by which some drugs cause weight gain is not fully understood but is thought to relate to their appetite-stimulating effects and/or their effects on metabolism. The most well known weight-inducing drugs are the anti-psychotic medications and the impact of these and other psychiatric medications on body weight has recently been reviewed.[18]

NOF guidelines for drugs that may cause weight gain

Antipsychotics:	Especially olanzepine (Zyprexa)
Antidepressants	Tricyclics, SSRIs, MAOIs, mirtazepeine (Zispin) and lithium
Corticosteroids	All corticosteroids may produce weight gain by two mechanisms: fat redistribution causing truncal obesity, buffalo hump and moon face, and fluid retention via mineralocorticoid effects
Oral contraceptive preparations:	Progestogenic compounds
β-blockers:	Not only do these agents cause weight gain, but they may restrict physical activity due to fatigue
Oral hypogylcaemics:	Numerous agents shown to increase weight. Most sulphonylureas (except glimepiride). Glitazones improve insulin sensitivity, but some cause weight gain despite improvements in visceral adiposity
Insulin	In adipocytes insulin promotes lipogenesis and inhibits lipolysis
Anticonvulsants:	Weight gain has been documented with some agents (phenytoin, sodium valporate). Topiramate (topomax) is weight neutral or may cause weight loss
Antihistamines	Many antihistamines may cause weight gain though these effects are more pronounced with older agents

Future drug treatments

There is a great deal of scope for the development of new agents for the treatment of obesity. This is a complex area of therapy and while advances are being made, there has been difficulty in replicating the observations from animal models to humans – for example, in the case of leptin. There is potential for development in drugs that increase energy expenditure, for example β3-adrenoceptor agonists, and also new centrally acting drugs, such as cholecystokinin receptor agonists.[19]

A new drug which is the final phase of clinical trial is Rimonabant or Acomplia. This is in a new class of drug entitled Selective CB_1 Blocker that blocks the CB_1 receptors in the endocannabinoid (EC) system. The EC system has a role in regulation of body weight and lipid metabolism and increased activity of the system is associated with excessive food intake, and fat accumulation as well as smoking. Rimonabant inhibits the increased activity of the system causing weight loss and substantial metabolic benefits. The RIO study followed patients for one year taking 20 mg rimonabant compared with placebo, and demonstrated a loss of 8.6 kg, compared with 2.3kg on placebo. Almost 75% of patients lost at least 5% of their body weight (compared with placebo; 27.6%) and 44.3% lost at least 10% (placebo; 10.3%).[20]

It seems likely that rimonabant will become a useful addition to the pharmacotherapy arsenal, and may have a particular role to play in avoiding weight gain in those people attempting to stop smoking.

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