

Options in the pharmacological management of morbid obesity

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Obesity is one of the most common medical problems worldwide and a risk factor for illnesses such as hypertension, diabetes, degenerative arthritis and myocardial infarction. It is a cause of significant morbidity and mortality and generates great social and financial costs.¹ WHO's latest projections indicate that globally in 2005, approximately 1.6 billion adults were overweight and that at least 400 million adults were obese.² Weight loss medications may be appropriate for use in selected patients who meet the definition of obesity or who are overweight with comorbid conditions. Medications are formulated to reduce energy intake, increase energy output or decrease the absorption of nutrients. Drugs cannot replace diet, exercise and lifestyle modification, which remain the cornerstones of obesity treatment.¹

Overweight and obesity are serious medical problems that affect over 55% of the adult population worldwide and

both require appropriate and effective management by suitably trained members of a multidisciplinary team.³ In Malta, 35% of

children aged between 7 and 11 years are overweight.⁴

The National Institute for Clinical Excellence (NICE) considers people to have morbid obesity if:

- they have a Body Mass Index (BMI) of 40 kg/m² or more or
- they have a BMI of between 35 kg/m² and 40 kg/m² and other significant disease (for example, diabetes, high blood pressure) that may be improved if they lose weight.⁵

The recognition of the health consequences of overweight and obesity, the benefits of modest weight loss and the frequent failure of lifestyle interventions for both weight loss and weight loss maintenance, has led to the search for effective pharmaceutical anti-obesity treatments.³

The initial treatment of obesity should focus on a diet and exercise program that has been individualized to the patient's lifestyle and physical needs. Behavioural therapy should be implemented as an adjunct to this program.⁶

Anti-obesity drug therapy is often useful as an adjunct for patients who cannot achieve sufficient weight loss through lifestyle and behavioural modification.³ A useful medication for obesity treatment must:

- be effective for body weight reduction and result in overweight-dependent conditions improvement;
- have long-term efficacy and safety;
- be related to tolerable or transitory side effects;
- not be addictive;
- have a known mechanism of action;
- be reasonably affordable.⁷

Anti-obesity drugs are classified on the basis of their mechanism of action – appetite suppression, altered nutrient absorption, or increased energy expenditure.⁶

Appetite suppression

Sibutramine is a norepinephrine and serotonin reuptake inhibitor which does not stimulate secretion of serotonin. The drug produces weight loss by two

mechanisms: sibutramine's central action on neurotransmitters results in early satiety with reported 20% reduction in food intake. Secondly, sympathetically mediated thermogenesis maintains original Basal Metabolic Rate which usually falls as weight is lost.⁷ Two studies have looked at the incidence of valvular heart disease and essentially did not report any difference between patients on sibutramine or placebo. Sibutramine 10 or 15 mg provided significantly greater weight loss than dietary advice alone in a 1-year study of 485 patients with a BMI of 27 to 40kg/m².⁶

The National Institute of Clinical Excellence reported in 2001 that randomised controlled trials found that sibutramine produced a dose-related weight loss when given in the range 5 – 30mg/day, with an optimal dose of 10 – 15 mg/day. Mean weight loss was greater with sibutramine than with placebo, on average by about 3 kg at 8 weeks, between 4 and 9 kg at 24 weeks and between 4 and 5 kg at 1 year. People who had lost weight on sibutramine

were more likely to maintain the loss when sibutramine use was extended than were those who were randomised to diet and exercise alone. Retrospective subgroup analysis found no statistically significant differences between men and women, or between ethnic groups in the effects of sibutramine treatment.⁹

Adverse effects attributed to sibutramine include headache, insomnia, constipation and dry mouth. Increases in blood pressure and pulse rate may also occur. Patients with cardiac conditions should be given this drug with caution. The manufacturer advises against giving sibutramine to patients with a history of coronary artery disease, congestive heart failure, arrhythmias or stroke.¹⁰

Altered nutrient absorption

Orlistat reduces the systemic absorption of dietary fat by potently and irreversibly inhibiting gastric and pancreatic lipases. These enzymes catalyse hydrolytic removal of triglycerides fatty acids and produce free

fatty acids and monoglycerides.⁶ Orlistat binds irreversibly to lipase active sites through covalent binding.⁸ By blocking these enzymes, triglycerides in dietary fat cannot be metabolized into absorbable free fatty acids and monoglycerols, and thus are excreted in the faeces.⁶ Studies have shown weight loss of 8.5% at one year compared with 5.4 % for placebo.¹ A study looking specifically at the effect of orlistat on obese adults with coronary heart disease risk factors (type 2 diabetes, hypercholesterolaemia or hypertension) found that more orlistat-treated patients than placebo recipients maintained a weight loss of > or equal to 5%. However, for a weight loss of > or equal to 10% there was no statistical difference between the placebo and treated groups.¹¹ The view that orlistat may be beneficial in patients with comorbid conditions related to obesity, such as diabetes and hyperlipidaemia is supported in several recent reviews. One review noted that in some long-term studies, orlistat-treated patients had

Table 1: Comparison of drugs licensed for the treatment of obesity ^{10,14,15}

	Orlistat	Sibutramine	Rimonabant
Presentation	120mg hard capsules	10mg and 5mg hard capsules	20mg film-coated tablets
Clinical Indications	Treatment of obese patients with a body mass index (BMI) greater or equal to 30 kg/m ² , or overweight patients (BMI ≥ 28 kg/m ²) with associated risk factors, in conjunction with a mildly hypocaloric diet.	As an adjunct to diet and exercise for the treatment of obese patients (BMI ≥ 30 kg/m ²), or overweight patients (BMI > 27 kg/m ²) with associated risk factor(s), such as type 2 diabetes or dyslipidaemia.	
Adult Dose	One 120 mg capsule taken with water immediately before, during or up to one hour after each main meal. If a meal is missed or contains no fat, the dose of orlistat should be omitted.	One capsule of 10 mg swallowed whole, once daily, in the morning, with liquid. The capsule can be taken with or without food. In those patients with an inadequate response to 10mg (defined as less than 2 kg weight loss after four weeks treatment), the dose may be increased to one capsule of 15mg once daily, provided that the 10mg dose was well tolerated.	One 20 mg tablet daily to be taken in the morning before breakfast.
Interactions	Ciclosporin Acarbose Fat soluble vitamins Oral anticoagulants Amiodarone	CYP3A4 inhibitors e.g. ketoconazole, itraconazole, ritonavir, telithromycin, clarithromycin, erythromycin and ciclosporin. CYP3A4 inducers e.g. rifampicin, phenytoin, Phenobarbital, carbamazepine and dexamethasone. Drugs which raise serotonin levels in the brain Simultaneous use of two SSRIs or an SSRI with certain antimigraine drugs or with certain opioids	

moderate decreases in diastolic blood pressure, insulin levels while fasting, and total cholesterol and LDL cholesterol, with a small cholesterol-lowering effect that was independent of weight loss.¹¹

Side effects of orlistat include steatorrhea, flatus, faecal incontinence and oily spotting. These effects are more dramatic with the consumption of fatty foods and may contribute to weight loss by discouraging dietary indiscretion. In two randomized controlled studies, gastrointestinal side effects were considered mild to moderate and improved in the second year of treatment.¹

Increased energy expenditure

Agents that increase energy expenditure are scarce. The search for a thermogenic medication that has a tolerable side effect profile has yielded few drugs, and none is recommended for weight loss treatment.¹ Ephedrine and the xanthines, such as caffeine and theophylline, increase metabolic rate. Studies have demonstrated their efficacy as short-term weight loss medications, but the risk of cardiac complications from hypertension, increased heart rate, increased myocardial oxygen consumption and increased cardiac output limit their clinical use.¹

Other drugs

Rimonabant

Rimonabant was the first selective cannabinoid-1 receptor blocker to enter clinical trials. In genetic and diet-induced obesity, rimonabant, reduces overactivation of the central and peripheral endocannabinoid system and prevents weight gain and associated metabolic disorders.¹² The results of a randomized, double-blind, placebo-controlled 2-year multicenter study suggest that 20mg per day of rimonabant is effective in reducing body weight and waist circumference, while also favourably affecting several cardiometabolic risk factors.¹² Most of these effects were dose-dependent. The RIO-North America trial concluded that compared with patients who received placebo, patients who received 20mg of

Practice Points¹⁶

- The aims of treatment for overweight and obesity should be modest weight loss maintained for the long term, with treatment methods and goals being decided for each individual after careful assessment of the degree of overweight and any associated co-morbid conditions.
- The first-line strategy is a combination of supervised diet, exercise and behaviour modification.
- Anti-obesity drugs may be used in adult patients at medical risk from obesity (BMI 30 or greater), or overweight patients with established co-morbidities (BMI 27) if the drug license permits.
- Not all obese patients respond to drug therapy. An anti-obesity drug should therefore be prescribed for no longer than 12 weeks in the first instance and weight loss should then be measured. The drug treatment should be stopped in those obese patients who have not achieved a 5% weight reduction after 12 weeks of treatment. If a 5% weight loss is attained then the drug may be continued beyond this initial period, provided body weight is continually monitored and weight is not regained.
- The duration of treatment with an anti-obesity drug must never exceed the time period recommended by the product license of the drug.
- Prescribers of anti-obesity drugs must be aware of their possible adverse actions. When assessing the suitability of a patient for drug treatment, it is important to consider the risk/benefit ratio, remembering that drug therapy is not without risk.
- All obese patients receiving drug therapy should be given regular review.

rimonabant had favourable changes in levels of HDL cholesterol, triglycerides, and fasting insulin that appeared to be approximately twice that expected from the achieved weight loss alone, suggesting a direct pharmacological effect of rimonabant on glucose and lipid metabolism beyond the weight loss achieved.¹³

In placebo-controlled studies, the discontinuation rate due to adverse reactions was 15.7 % for patients receiving rimonabant and the most common adverse reactions resulting in discontinuation were: nausea, mood alteration with depressive symptoms, depressive disorders, anxiety and dizziness.¹⁴

Over the counter (OTC) products

A number of OTC products are advertised as treatments for weight loss. Patients and physicians should be aware that such products are packaged in uncertain dosages and are usually of uncertain potency and purity. This in turn can lead to unpredictable therapeutic and adverse effects. Thus, the treatment of choice for patients with a low risk of

obesity is not OTC products but dietary intervention accompanied by exercise and behavioural modification.

Treatment considerations

Most antiobesity medications produced 5% to 10% weight loss in clinical trials, which is likely to be of significant medical benefit even if the patient has not reached his or her desirable body weight. Obesity is a chronic disease, as evidenced by the high likelihood of weight regain, and consequently a long-term approach to treatment is needed.⁶

Clinicians must learn to recognize treatment failure and alter the drug therapy regimen. Patients who do not lose at least 4lbs during the first 4 to 8 weeks of therapy should be considered non-responders to that medication. In this situation, the medication should be stopped and another anti-obesity drug should be considered. Table 1 gives a comparison of drugs licensed for the treatment of obesity. Once a patient has lost a significant amount of weight, it becomes important to sustain the weight loss.⁶

Conclusion

Obesity is recognized as an epidemic condition that affects populations worldwide. Therefore, the need to improve the quality and efficacy of therapeutics has emerged. The core to current obesity management is based on specific behavioural therapies aiming to

change eating habits and raise energy expenditure, nutritional counseling to lower the intake of calories, particularly fat as well as increased daily physical activities.

Pharmacological management is seen as an additional tool to this basic therapy in those patients where dietary

and lifestyle modifications have proved unsuccessful. The thoughtful use of medications for the management of obesity can be valuable for many patients, however, no medication alone will solve the problem of obesity and no medication should be used as a substitute for the development of healthier adults.

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