

REVIEW ARTICLE

Current medical management of obesity

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ABSTRACT

The International Obesity Task Force estimates that more than 300 million individuals worldwide are obese and an additional 800 million are overweight. Weight loss between 5-10% of initial bodyweight is associated with improvements in cardiovascular risk profiles and reduced incidence of type 2 diabetes. Three major drug options for the long-term treatment of obesity are orlistat and sibutramine and rimonabant. The longest duration of treatment in clinical trials is 4 years for orlistat and 2 years for sibutramine and rimonabant. Orlistat, a gastrointestinal lipase inhibitor, reduces weight by around 3 kg on average, improves cardiovascular risk factors and decreases progression to diabetes in high-risk patients; adverse gastrointestinal effects are common. Sibutramine, a monoamine-reuptake inhibitor, results in mean weight losses of 4–5 kg, but is associated with increases in blood pressure and pulse rate. The risk-benefit of sibutramine, is being assessed in a large study of cardiovascular outcomes. Rimonabant, the first of the endocannabinoid receptor antagonists, reduces weight by 4–5 kg on average and improves waist circumference and concentrations of HDL cholesterol and triglyceride; however, an increased incidence of mood-related disorders has been reported. The combination of medication and group lifestyle modification resulted in more weight loss than either medication or lifestyle modification alone. [IJEM 2007;11(1&2):37-41]

Keywords : Obesity, body mass index, Sibutramine, Orlistat, Rimonabant

The International Obesity Task Force estimates that more than 300 million individuals worldwide are obese and an additional 800 million are overweight(1). The pathophysiology of obesity is complex and poorly understood, but it includes genetic, behavioral, physiological and other factors(2). A recent study reported that among people who carried a single copy of the high risk allele for the FTO gene, which is associated with fat mass and obesity, the risk of obesity increased by 30%. The risk of obesity increased by 67% among people who carried two allele, and on average they gained 3.0 Kg or more(3).

For the first time, the number of overweight individuals in the world is equivalent to the number underweight(4). Unless these trends are reversed, the health-related consequences will be serious. The current methods for lifestyle modification alone, as a treatment for obesity are widely regarded as ineffective.

Anti-obesity pharmaco-therapy is an important adjunctive treatment to lifestyle modification. The ideal anti-obesity drug has three important characteristics.

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First, it should cause sustained clinically significant reductions in bodyweight and reduce obesity-related morbidity and mortality. Second, the benefit-risk ratio of the drug must be favorable. The track record for safety of anti-obesity drugs has been particularly poor,(6) whereas their potential for abuse by non-obese individuals striving to lose weight is high(5). Third, affordability(7).

The indications for drug therapy(7,8)

Patients with a body-mass index (BMI) of 30 kg/m² or greater or a BMI of 27.0-29.9 kg/m² with a other comorbid conditions (e.g. Diabetes, hypertension, obstructive sleep apnea) are currently deemed eligible for antiobesity drug treatment.

Weight loss between 5-10% of initial bodyweight is associated with improvements in cardiovascular risk profiles and reduced incidence of type 2 diabetes(7,8). Therefore, as a general guideline for weight reduction, a 10% weight-loss is recommended.

Three major drug options for the long-term treatment of obesity are currently approved. These drugs are: orlistat and sibutramine and rimonabant.

Orlistat

Orlistat was approved in 1998. It is a gastric and

Table 1: Pharmacological properties of sibutramine, orlistat, and rimonabant

	Sibutramine	Orlistat	Rimonabant
Mechanism of Action	Monoamine-reuptake inhibitor (primarily norepinephrine and serotonin)	Gastric and pancreatic lipase inhibitor	Endocannabinoid (CB1) receptor blocker
Typical dose	10-15 mg once daily	120 mg twice daily with meals	20 mg daily
Absorption	77%	Minimal	Not Known
Plasma protein binding	94%	99%	99.9%
Time to peak concentration	1-2h (2.5-3.6 h for metabolites)	8 h	2 h
Metabolism	Primarily via hepatic cytochrome 3A4 enzymes to active M1 and M2 metabolites	Some metabolism within gastrointestinal wall to inactive metabolites	Hepatic cytochrome 3A4 and aminohydrolase pathways to inactive metabolites
Elimination	Primarily urine (77% drug ingested; 83% unchanged)	Faeces (over 96% of total)	Biliary excretion and faecal elimination (86%)
Elimination half-life	1.1 h (M1 metabolite, 14h; M2 metabolite, 16 h)	14-19 h	6-9 days (16 days in obese patients)

pancreatic lipase inhibitor that reduces dietary fat absorption by around 30%(9). The compound is a partly hydrated derivative of an endogenous lipstatin produced by *Streptomyces toxytricini*(10). Typically 120 mg three times daily is prescribed with meals; 60 mg orlistat is also currently available. Because of low systemic absorption and first-pass metabolism, the bioavailability of orlistat is less than 1%. Most of the drug is excreted unchanged in faeces.

Efficacy: In a 4-year double-blind placebo-controlled randomized study of 3305 obese patients, orlistat reduced weight by 2.7 kg on average and decreased the incidence of type 2 diabetes from 9.0% to 6.2%(11). Only 43% of patients completed this study and the beneficial effects were almost all in patients with impaired glucose tolerance at baseline. In a meta-analysis of 11 placebo-controlled trials of 1 year in 6021 overweight or obese patients, orlistat reduced weight by 2.9%(12). The number of patients reaching 5% and 10% placebo-subtracted weight-loss thresholds was 21%(19-24%) and 12% (8-16%) greater with orlistat than with placebo. Orlistat also reduced blood pressure by 1.8 mm Hg systolic (0.9-2.6 mm Hg) and 1.6 mmHg diastolic (0.7-2.4 mm Hg), LDL cholesterol by 0.27 mmol/L (0.22-0.31 mmol/L), and fasting glucose in patients with diabetes by 0.8 mmol/L (0.3-1.3 mmol/L). No clinically significant effects on triglycerides or HDL cholesterol were seen. Drop out rates were high, averaging 33%. Other than diabetes incidence, there are no long-term outcome data showing that orlistat reduces major obesity-related morbidity and mortality.

Adverse effects: The major adverse effects with orlistat are gastrointestinal. Fatty and oily stool, faecal urgency, and oily spotting occurred in 15-30% of orlistat-treated patients (2-7% with placebo). Faecal incontinence was

observed in 7% of orlistat-treated patients compared with 1% of those on placebo(13). To prevent possible deficiencies of fat-soluble vitamins, co-prescription of a daily multivitamin is recommended. Orlistat can reduce the absorption of amiodarone(14) and cyclosporine(15) and can potentiate the effect of warfarin(16). Systemic adverse effects are minimal because of the lack of systemic absorption.

Sibutramine

Sibutramine is a centrally acting mono-amine-reuptake inhibitor that mainly acts to increase satiety(17) Sibutramine also stimulates thermogenesis; however, this secondary action plays a minor part in weight reduction(18). The drug was approved in the USA in 1997 and in the European Union in 1999. Sibutramine undergoes extensive first-pass metabolism, mainly by hepatic cytochrome p450 3A4 enzyme, to active primary (M1) and secondary (M2) amine metabolites, which are more potent than the parent compound(17). Most of the drug and its active metabolites are renally excreted.

Efficacy: In three randomized double-blind, placebo-controlled weight-loss trials of 1 year, in 929 overweight or obese patients, sibutramine reduced weight by 4.6% (95% CI 3.8-5.4%)(12). Drop out rates in these three trials averaged 48%. The number of patients reaching 5% and 10% placebo-subtracted weight-loss thresholds was 34% (28-40%) and 15% (4-27%) greater with sibutramine than with placebo. In long-term studies, sibutramine had little effect on concentrations of LDL cholesterol and on glycaemic control, and had conflicting effects (no change to mild improvement) on concentrations of triglyceride and HDL cholesterol(13).

Efficacy of sibutramine is greatly enhanced when used with intensive lifestyle modification and regular

frequent follow-up visits. In a 1 year randomized trial, 224 obese adults received sibutramine alone, sibutramine plus brief individualized lifestyle modification, group lifestyle modification alone (30 sessions), or sibutramine plus 30 sessions of group lifestyle modification(19). Those in the lifestyle modification plus sibutramine group lost the most weight, an average 12.1 kg compared with 5.0 kg with sibutramine alone (mean difference 7.1 kg, estimated 95% CI 3.9-10.2 kg). As with orlistat, long-term data on the effect of sibutramine on major obesity-related morbidity and mortality are lacking. However, the ongoing Sibutramine Cardiovascular Outcomes (SCOUT) trial is assessing the efficacy of sibutramine in reducing myocardial infarction, stroke and cardiovascular mortality in 9000 obese and overweight patients. This study should finish in 2008(20).

Adverse effects: Common side-effects include insomnia, nausea, dry mouth and constipation. By contrast with fenfluramine and dexfenfluramine, sibutramine does not increase release of serotonin and has not been associated with valvular heart disease or pulmonary hypertension (21). Concomitant treatment with monoamine-oxidase inhibitors or serotonergic drugs is also not recommended because of the potential risk of serotonin syndrome. Furthermore, sibutramine has been associated with small increase in blood pressure and pulse rate, leading to concerns about potential cardiovascular toxic effects. An independent review concluded that sibutramine had a favorable risk-benefit ratio. However, the drug is not recommended in patients with uncontrolled hypertension, pre-existing cardiovascular disease or tachycardia(22).

Rimonabant

The ability of recreational marijuana to reliably stimulate appetite generated interest in the use of endogenous cannabinoid agonists and antagonists for weight-related disorders. The endocannabinoid system includes two major receptors, the CB1 and CB2 receptor, and two major ligands, anandamide and 2-arachidonoylglycerol (2-AG)(23). Endocannabinoids are polyunsaturated phospholipid-derived eicosanoids produced on demand(24) from arachidonic acid that elicit many biological responses, including counteracting stressful stimuli such as food deprivation, aversive memories, and pain(25). In the brain, endocannabinoids act in a retrograde manner and are rapidly cleared. The CB1 receptor is a G-protein coupled receptor that is extensively expressed in the CNS, including in areas vital to the control of food intake(26). Endocannabinoids interact with several anorexic and orexigenic pathways within the CNS, including the central melanocortin and mesolimbic pathways, increasing motivation to eat and stimulating food intake(26).

Rimonabant, the first CB1-receptor blocker, was initially intended as an antiobesity and smoking-cessation dual-purpose drug; however, the latter development programme has been discontinued. Rimonabant is a

potent CB1-selective ligand, with 1000-fold greater affinity for the CB1 receptor than the CB2 receptor(27). The drug is hepatically metabolized and excreted in bile. Because of a larger peripheral volume of distribution, obese individuals have a drug half-life that is twice as long (16 days) as non-obese people(28). Rimonabant produces a dose-dependent reduction in food intake in various rodent models(29), effects that seem to be both centrally and peripherally mediated. Potential peripheral mechanisms include enhanced thermogenesis via increased oxygen consumption in skeletal muscle,(30) diminished hepatic(31) and adipocyte lipogenesis,(32) augmentation of adiponectin concentrations, promotion of vagally mediated cholecystokinin-induced satiety, inhibition of preadipocyte proliferation and increased adipocyte maturation without lipid accumulation(34).

Efficacy: Four double-blind trials, comprising the Rimonabant In Obesity (RIO) Program, compared rimonabant 5 mg or 20 mg daily with placebo in more than 6600 individuals. RIO-Europe, RIO-Lipids, RIO-North America(35), and RIO-Diabetes(34) have published 1 year results. RIO-North America also included a second year of follow-up in which rimonabant-treated patients were re-randomised to continue active drug treatment or switch to placebo. The RIO Program enrolled patients with BMIs of 30 kg/m² or greater or BMIs of higher than 27 kg/m² with dyslipidaemia (predominantly high triglyceride or low HDL cholesterol concentrations), type-2 diabetes or hypertension. Middle-aged women were most commonly included and enrolment was restricted to highly selected and adherent patients without major comorbidity. Dropout rates at 1 year averaged 40-50%, similar to studies of orlistat and sibutramine(13). Compared with placebo, rimonabant significantly reduced weight by 4.6 kg (95% CI 4.3-5.0), reduced waist circumference, and improved triglyceride and HDL cholesterol profiles. The proportion of patients achieving 5% and 10% placebo-subtracted weight loss was 29-39% and 17-25% higher with rimonabant treatment than with placebo ($p < 0.001$ in all cases)(33,35). In RIO-North America, rimonabant-treated patients re-randomised to placebo in year 2 regained weight, whereas those who continued to receive the 20 mg dose maintained their weight loss(35). Compared with placebo, rimonabant also significantly reduced the placebo-subtracted incidence of metabolic syndrome in all four trials and the placebo subtracted HbA1c by 0.7% ($p < 0.001$) in RIO-Diabetes(34). Concentrations of LDL cholesterol did not improve and blood pressure was either unchanged or slightly reduced. No data on cardiovascular morbidity or mortality have been reported, but several rimonabant studies examining clinical endpoints and surrogate measurements of atherosclerotic burden (e.g. intravascular ultrasound) are underway(36,37). The largest is the Comprehensive Rimonabant Evaluation Study of Cardiovascular Endpoints and Outcomes (CRESCENDO) trial,(38) which is investigating the effect of rimonabant on

myocardial infarction, stroke, and cardiovascular death in 17000 obese participants.

Adverse effects: The most frequent adverse events are nausea, dizziness, diarrhoea, and insomnia, each occurring 1-9% more frequently than with placebo. Side-effects leading to drug discontinuation occurred in 13-16% of patients taking the 20 mg dose(33,34). In RIO-Europe, RIO-North America and RIO-Lipids, drug discontinuation due to psychiatric disorders (mainly depression) occurred in 6-7% of rimonabant-treated individuals, an absolute increase of 2-5% over placebo.

How to choose an antiobesity drug?

There are no definitive data showing benefit of one antiobesity drug over another and all three drugs are limited by modest efficacy and low rates of persistence with treatment. Therefore, if drug treatment is to be started, the initial choice is largely based on patients preference, associated cardiovascular risk factors, and adverse effects. Individual drug-plan and costs are also important. Without definitive head-to-head trials, we suggest the following approach to initial pharmacotherapy on the basis of our review of the evidence and clinical experience.

Orlistat reduces LDL concentrations and diabetes incidence, is associated with slight reduction of blood pressure, and is not associated with major systemic toxic effects. Thus this drug might be especially useful in patients at high risk for developing type 2 diabetes, with high LDL cholesterol concentration or with pre-existing cardiovascular disease. Orlistat should be avoided in patients with chronic diarrhoea.

Sibutramine, because of its satiety-enhancing effects, might be beneficial in cases where a lack of satiety or frequent snacking is a major barrier to weight reduction. Until further efficacy and safety data are available, sibutramine should be avoided in patients with poorly controlled hypertension, pre-existing cardiovascular disease or tachycardia.

Rimonabant may be considered in patients with dyslipidaemia associated with the metabolic syndrome (low HDL cholesterol and high triglyceride concentrations) and in patients who are concurrently attempting to stop smoking. The drug should be used with caution in patients with pre-existing psychiatric illness, particularly depression or anxiety, and in those with liver impairment.

Irrespective of which drug is initially selected, treatment should be discontinued if clinically significant weight loss (i.e. at least 5-10% of initial bodyweight or improvement in major obesity-related comorbidity) does not occur within the first 3-6 months. Combination treatment has not been well researched and the existing evidence does not suggest significantly greater weight loss than with single-drug treatment(39,40). Furthermore, the optimum duration of treatment is unclear. The longest duration of treatment in clinical trials is 4 years for orlistat and 2 years for sibutramine and rimonabant. Because drug

discontinuation invariably leads to weight regain, if clinically significant weight loss is achieved, longer courses of treatment are reasonable to consider.

The combination of medication and group lifestyle modification resulted in more weight loss than either medication or lifestyle modification alone.

Future Drugs

Many other novel potential antiobesity drugs and targets have been identified, including those acting on the central melanocortin pathway, a group of neurons centered in the arcuate nucleus and hypothalamus that control appetite and energy expenditure(41). Examples include ciliary neurotrophic factor and other melanocortin-4 receptor agonists, ghrelin, neuropeptide Y antagonists, melanin-concentrating hormone antagonists, and peptide YY. Although newer drugs are years away from clinical use, the hope for research investments made to date is translation into safe and effective anti-obesity drugs in the future. The neurobiology of obesity is extremely complex, with many overlapping and redundant pathways. This complexity decreases the probability that targeting any single pathway will result in dramatic weight loss and suggests that multiple drugs with different mechanisms will be needed to produce significant and persistent weight loss. The search for novel drug treatments for obesity is necessary. However, efforts to fill the therapeutic void that characterizes contemporary obesity management, the benefits of obesity pharmacotherapy must outweigh the risks and costs.

CONCLUSION

Orlistat and sibutramine produce average placebo-subtracted weight losses of less than 5%. Orlistat improves cardiovascular risk factors and reduces diabetes incidence in high-risk individuals. The risk-benefit of sibutramine, which can increase blood pressure, is being assessed in a large study of cardiovascular outcomes. Rimonabant is the first of the endocannabinoid receptor antagonists. The weight loss induced by rimonabant appears similar to that of sibutramine, and improvements in HDL cholesterol and triglyceride concentrations have been reported. An increase in the incidence of psychiatric disorders was observed in rimonabant-treated patients. The lack of cardiovascular morbidity and mortality endpoints in obesity drug trials represents a major gap in knowledge. Other endpoints, such as osteoarthritis, gastro-oesophageal reflux disease, sleep apnea, and quality of life, have also been neglected.

Except bariatric surgery, which is neither a feasible nor a desirable population-based treatment for obesity, no intervention has produced consistent effective long-term weight loss. Treatments targeted at the individual are important, but equally essential, is the need to elicit changes in society that address all aspects of the environment thought to be obesogenic. To be successful, such initiatives should involve the concerted efforts of all,

from policy makers to the food and drug industries, and from educators to patients and physicians. Even if lifestyle and population-based strategies are creatively and successfully implemented, the large burden of prevalent obesity dictates that many will remain at risk for obesity-related comorbidity and premature death.

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