

# Obesity: Which Drug and When?

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## Summary and Introduction

### Summary

**Background:** Obesity, with all its consequences, is audaciously confronting medical professionals and health service providers worldwide. Diet and exercise intervention is an essential part of any weight management strategy, but may not succeed in isolation. Effective approaches for routine practice are more likely to involve affordable, efficacious and well-tolerated drug therapy than the more expensive, case selective approach of bariatric surgery.

**Objectives and Conclusions:** Advancement of pharmacotherapy is expanding the battery of available drugs; the clinician is faced with an increasingly complex therapeutic decision. Which drug to use, and when, is influenced by a range of factors, discussed here. There is a large body of high quality evidence in the literature to support the presently available drugs; however, many questions remain unanswered including duration of therapy and whether longer-term goals of improved morbidity and mortality are achievable. Clinician and patient awareness of these issues will provide a more informed therapeutic decision and ultimately improve the potential for reaching the weight management targets.

### Introduction

**The Obesity Epidemic.** Present trends predict that by 2010, one-third of adults in the UK will be obese<sup>[1]</sup>. Obesogenic traits of westernised society had reached every corner of the globe and the problem has reached pandemic proportions. Worldwide, the World Health Organisation indicates that there were at least 400 million obese adults in 2005; by 2015, this will have almost doubled to 700 million. The nature of global malnutrition is changing with as many people now suffering from overnutrition as those under-nourished. The costs to society are incalculable. Rising levels of comorbidity affecting nearly every organ system in the body have outstripped improvements brought about by advances in public health and medical care and declining smoking rates, potentially causing a decrease in life expectancy in developed countries for the first time.

### Modalities of Treatment: The Role of Pharmacotherapy

No single treatment modality is independently effective in the management of obesity. Intervention is unlikely to be effective if it is not tempered with strategies to enable the patient to make permanent life-style changes. It is a common misconception that drug therapy alone will control this problem. Motivated patients can achieve remarkable degrees of sustained weight loss with dietary change and exercise alone; however, they represent the minority, and it is clear that this idealistic approach will not address the

global obesity problem. Bariatric surgery can produce impressive long-term weight loss, survival advantage, improvement in quality of life and reduced cardiovascular risk factors <sup>[2,3]</sup>. However, only a subset of patients are eligible for surgery and financial constraints ultimately cap this service. Pharmacotherapy does have the potential to infiltrate a large proportion of the obese population and recent advances are raising the profile of anti-obesity medication. Given sufficiently early, drug treatment for obesity has the potential to prevent the multiple medical and polypharmacy consequences of obesity.

### **Tools of the Trade: Available Drugs**

There are three drugs with adequate efficacy and safety data from long-term (1-4 years) randomised controlled trials, now licenced in Europe for weight management. Orlistat has been available since 1998, with sibutramine approved in the EU in 1999, and rimonabant in 2006. An understanding of the mode of action of these drugs is helpful in making the most appropriate choice for each patient.

### **Therapeutic Decisions**

Obesity, like many chronic medical disorders often presents a complex interplay of psychology, environmental factors, physiology and pathological processes of disease. The morbidly obese patient has reached their present state because of a multitude of factors - every patient is unique, and an understanding of the sequence of events will produce a more informed management plan. The two most common clinical questions related to obesity medication are first which drug to use, and second when.

### **Which Drug? - Factors to Consider**

#### **Efficacy - Outcome Measures/treatment Goals**

With all drugs, there are patients who do not respond, but excluding this 10-20% identifiable after 4-8 weeks, drug therapy for obesity typically produces 5-10% weight reduction when added to dietary and lifestyle change <sup>[7]</sup>. In terms of absolute weight loss, the presently available drugs are roughly equivalent; however, head-to-head clinical studies have not been undertaken, and it is unlikely that the Pharmaceutical Industry will be enthusiastic to conduct this type of research. Weight loss targets for anti-obesity medication may confuse rather than clarify expectations. The European Medicines Agency proposes a minimum target weight loss of 10% at 1 year compared with baseline, with statistically greater weight loss in intervention subjects compared with placebo, but no value of the magnitude of difference between placebo and treatment arms is suggested <sup>[8]</sup>. The Food and Drug Administration target is more specific, suggesting weight loss in the treatment group that is statistically significantly greater than placebo by at least 5% <sup>[9]</sup>. Interpretation of efficacy based on the available evidence is further complicated by high attrition rates in many of the studies, and inclusion of weight loss during the placebo run-in period, potentially overestimates the drug effect <sup>[10]</sup>.

Beneficial effects of drug therapy may be underestimated if absolute weight loss is the only focus. Modest weight loss of this magnitude does produce a health dividend with reduction in the development of type II diabetes and improved cardiovascular outcomes. The strength of evidence for these outcomes may influence the choice of drug. The evidence for improved glycaemic control is strongest for orlistat, with a risk reduction of 37% in the incidence of diabetes over 4 years (9.0% cumulative incidence in placebo vs. 6.2% with orlistat) in the XENical in the Prevention of Diabetes in Obese Subjects trial<sup>[11]</sup>. There may also be a small reduction in low-density lipoprotein (LDL) cholesterol with orlistat. Sibutramine has little effect on LDL cholesterol, but may improve triglycerides and high-density lipoprotein (HDL) cholesterol profiles<sup>[12]</sup>. Rimonabant, through its dual activity - centrally in the regulation of appetite and intake, and peripherally in the liver, adipose tissue and skeletal muscle, has demonstrated improvements in triglycerides, HDL cholesterol and HBA<sub>1</sub>C in diabetics. Benefits have also been shown in terms of reduction of the incidence of metabolic syndrome, characterised by the co-existence of hypertension, dyslipidaemia, increased waist circumference and impaired glycaemic control [rimonabant in obesity studies (RIO)]<sup>[13-16]</sup>. Interestingly, none of these drugs alone is effective in reducing blood pressure elevated by obesity. In the case of sibutramine, this has been attributed to its noradrenergic actions. Blood pressure does fall acutely when weight loss is achieved in hypertensive, obese patients treated with sibutramine; however, the magnitude of fall in blood pressure is greater in patients who achieve the same degree of weight loss on placebo<sup>[17]</sup>. The fact that rimonabant has little effect on blood pressure suggests that the hypertension associated with obesity may reflect a permanent re-setting of neuroendocrine regulation. A primary preventative effect on hypertension following bariatric surgery was not supported by the 10-year Swedish Obese Subjects study<sup>[2]</sup> and a substudy suggested that initial decreases in the blood pressure after surgery may relapse during the follow-up<sup>[18]</sup>.

Present evidence points to a reduction in cardiovascular disease with anti-obesity drugs<sup>[19]</sup>. Studies are underway, but we do not yet know for sure whether any of these drugs have a significant impact on obesity-related mortality and morbidity<sup>[20,21]</sup>. These long-term data will be crucial for assessing the place of these drugs in the future. Other important prognostic outcomes, not yet fully assessed include respiratory conditions such as obesity hypoventilation and obstructive sleep apnoea. Pharmacological intervention for obesity may influence the course of these conditions and until this has been evaluated, we may be underestimating the benefits of these drugs. It is important to recognise that there are multiple benefits from effective weight management and that the primary aim of treatment is not restricted to cardiovascular risk reduction.

### **Adverse Effects, Interactions and Contraindications**

Orlistat undergoes minimal systemic absorption (bioavailability < 1%) and its potential for side effects and the interaction with other drugs and medical conditions is therefore very low<sup>[22]</sup>. It can reduce absorption of both cyclosporine<sup>[23]</sup> and amiodarone<sup>[24]</sup>, and extra anticoagulant monitoring is suggested because of a potential increased anticoagulant effect with warfarin<sup>[25]</sup>; these potential problems would very rarely preclude its use. Concomitant use with acarbose is not advised. From the patient's perspective, the 'side effects' of orlistat simply herald a failure to make sufficient dietary

changes. Excessive unabsorbed fat in stools is likely to cause flatus, loose bowel motions, increased frequency of defecation, faecal urgency and even faecal incontinence. Some patients may find it difficult to reduce their fat consumption to a level sufficient to tolerate orlistat. The use of orlistat is unadvisable in chronic malabsorption states; however, these patients are unlikely to be obese. Orlistat is unlikely to have a significant impact on the symptoms attributed to irritable bowel syndrome, if it is used correctly. Malabsorption of the fat soluble vitamins A, E, D and K, can occur <sup>[26,27]</sup> and supplementation may be advisable with prolonged use <sup>[28]</sup>, but blood concentrations seldom reach deficiency levels if good dietary advice is provided.

Sibutramine, acutely through its noradrenergic effects, causes a minor rise in pulse rate of the order of 1-2 bpm, and a small rise in blood pressure of the order 4 mmHg <sup>[12]</sup>. For this reason, its use is not recommended in uncontrolled hypertension or in patients with tachyarrhythmias. Controlled hypertension does not preclude use, and, if there are borderline concerns regarding blood pressure control, it may be acceptable to start the medication at the lower (10 mg) dose, and carefully monitor the blood pressure. A weight loss effect may offset any pro-hypertensive action and allow the drug to be tolerated. Extra care should be employed in such patients when considering a dose increase. There is now evidence that the weight loss and metabolic benefits of sibutramine are protected in the context of combinations of angiotensin converting enzyme (ACE) inhibitors and calcium channel antagonists, but that these effects may be diminished if thiazide and  $\beta$ -blocker regimens are used to control blood pressure <sup>[29]</sup>. Antihypertensive treatment should therefore be reviewed when considering sibutramine. These cardiovascular effects of sibutramine raise questions about its long-term benefits in terms of cardiovascular morbidity. Sibutramine Cardiovascular Outcome Trial (SCOUT) will further assess this <sup>[21]</sup>. The central action of sibutramine as a serotonin + noradrenalin reuptake inhibitor (SNRI) means that it cannot be used concurrently with selective serotonin reuptake inhibitor (SSRI) and monoamine oxidase inhibitor (MAOI) antidepressants and it is contraindicated in patients with major psychiatric disease. Depression is often inexorably linked to obesity - many patients suffer from low mood and poor self-esteem because they are obese, and conventional antidepressants are often ineffective. In such cases, it is reasonable to consider tailing off antidepressant therapy and commencing sibutramine which may itself provide a minor antidepressant effect. This can be predicted by sibutramine's mechanism of action, which is similar to tricyclic antidepressants, although its clinical efficacy in this respect has never been fully established <sup>[30]</sup>. This approach would not be acceptable where there is a clear history of major endogenous depression, unrelated to the development of obesity. Other minor side effects reported with sibutramine include nausea, constipation, dry mouth, agitation and insomnia. These effects are more common when commencing treatment, are usually self-limiting and rarely result in the treatment withdrawal. Weight loss alone may produce similar symptoms, especially in the absence of adequate water or fibre intake. Dietary advice is again vital.

Rimonabant, through its action on the endocannabinoid system, can influence mood. In the RIO studies, 2-5% more patients in the rimonabant arm vs. placebo withdrew from the treatment because of psychiatric side effects. Depression was the most common feature. These studies excluded patients with depression, and it is possible that this

effect has been underestimated. Patients with psychiatric problems, or those taking treatment for a psychiatric condition including antidepressants should not be prescribed rimonabant, and in patients without these concerns, it is prudent to monitor for any effects on mood. The drug is generally well tolerated; other side effects are minor and self-limiting. Rimonabant is metabolised in the liver, and should be used with caution in the context of liver disease. Similarly, co-administration of CYP3A4 inhibitors such as ketoconazole causes increased exposure to rimonabant.

## **Patient Preference**

The effectiveness of any drug therapy is largely determined by patient satisfaction and compliance. This is even more important in anti-obesity therapy, where patient motivation to comply with a multitude of dietary and lifestyle modifications, in addition to remembering to take their medication, is the key to success. By the time patients reach a tertiary referral centre they may already have received several medications. Their prior experience may not have been a positive one - the mode of action and potential side effects of the drug may not have been explained, and they may not have been provided with any dietary or exercise advice. This scenario leaves orlistat in a very vulnerable position and it is not surprising that patients may report a difficult experience. Working with, and understanding the patient's prior experience may allow a re-trial, with appropriate support. The motivation, advice, proactive support programme (MAP) programme provided by the manufacturers of orlistat is one such support programme. The best outcome in routine primary care is achieved with a structured diet and lifestyle programme, for example the Counterweight programme<sup>[31]</sup>.

Taking the patient's lifestyle into consideration allows an assessment of potential problems that might result in treatment non-compliance. Patients on a very high fat diet may be simply unable to make sufficient change to allow tolerance of orlistat, and may stop the medication or learn to manipulate treatment as their experience with the drug develops. Coupled with a busy lifestyle where rapid access to a toilet is not possible, such as with a travelling salesperson, the chances of treatment success are low. Identifying such problems at an early stage might direct the prescriber to a centrally acting therapy.

## **Cost Effectiveness**

There is little doubt that obesity is a drain on any nation's healthcare budget. Quantifying it in exact terms is very difficult considering the impact of obesity not just on prescribing budgets and primary and secondary healthcare, but also including the costs of social support services, loss of earning potential, incapacity and unemployment benefits. The cost effectiveness of drug therapy can be estimated in terms of the prescribing cost of the drug per quality adjusted life year gained. In the UK, the National Institute for Clinical Excellence (NICE) considers a drug cost effective when this sum lies between £19,000 and £55,000. Patients with multiple comorbidities as a result of obesity are likely to represent the most cost effective group, with a sum of around £2350 for orlistat in obese diabetics with hypertension and dyslipidaemia<sup>[32]</sup>. This suggests cost efficiency; it may be less clear-cut in patients with obesity alone, although long-term studies may provide

more information. The picture is further complicated when cost estimations have included non-responding patients who would normally have had their drug stopped after 4-8 weeks. Such estimates provided by NICE are therefore likely to exaggerate cost.

## **When to Use the Drug?**

### **When Should Drug Therapy be Considered?**

Current NICE guidelines recommend that anti-obesity medication be considered if patients have failed to reach their target weight loss, or reached a plateau after employing dietary and lifestyle changes. In some cases where there is an urgent medical need for the patient to lose weight, and depending on previous attempts to lose weight, medication may be considered at the first consult. Patients may specifically ask to be started on anti-obesity medication; an understanding of what is motivating the patient can be very helpful. Misconceptions about drug therapy can be addressed and an informed decision made. Any decision must follow a full discussion with the patient about the risks and benefits of such medication.

### **Weight Loss vs. Weight Maintenance**

Much of the focus of weight management centres on weight loss, however for some patients the therapeutic benefit of aiming for at least weight maintenance should not be underestimated. Obese people tend to continue to gain 1-2 kg per year, and halting this progression is likely to provide long-term benefits. Licencing restrictions based on successful weight loss prior to treatment, for example with orlistat, have to be considered in the context of the individual patient.

### **Duration of Treatment**

The effect of prolonged therapy with anti-obesity medication is not yet known, although studies are starting to suggest long-term benefit. Licencing restriction of 1-2 years, not evidence based in terms of safety or lack of efficacy, often lead to drug withdrawal. Weight regain is likely, usually rapid, and often associated with the loss of any improvements in the medical consequences of obesity, brought about by drug therapy. The use of medication for longer periods, 'off-licence' should be fully discussed with patients, and close follow-up is recommended. A common practice in primary care is to stop an anti-obesity drug once weight has fallen and reached a plateau, even before present licencing restrictions would apply. Again, weight regain is likely and the patient will not gain the benefit of long-term maintenance at a lower weight.

Stopping medication may be necessary if the patient has failed to lose weight. However, medication is often not continued long enough to make a reasoned decision. Patients started on sibutramine should be given at least 3 months before the treatment is abandoned because of failure. Diabetic patients offer a further complication, as they tend to lose weight more slowly, and extending this trial period to 6 months may be more helpful <sup>[33]</sup>.

## Special Cases

Pregnant and breast-feeding mothers should not be prescribed anti-obesity medication. In children, adolescents and the elderly people, there are limited data and caution, especially with centrally acting agents, should be employed. Weight loss is seldom advisable in growing, developing children. Exceptions may be made by specialists for extreme and complicated cases.

## Clinical Trials

Access to clinical trials can prove very useful to patients, especially if they have exhausted all other avenues for weight management. Often the intense experienced dietary support offered during the study provides the key incentive so often omitted from drug treatment in primary care. Patients will often lose weight on treatments they have previously failed with.

Table 1.

Medscape®		www.medscape.com
Orlistat (4)	Sibutramine (5)	Rimonabant (6)
Intestinal lipase inhibitor	Serotonin + noradrenalin re-uptake inhibitor	Endocannabinoid (CB1) antagonist
Malabsorption of 30% of dietary fat: equivalent in a low fat diet (< 60 g fat/day) to 180 kcal/day	Central nervous system (CNS) effects to increase satiety	CNS effects to increase satiety and patterns of eating
	May stimulate thermogenesis in brown adipose tissue (minor effect)	Peripheral effects on hepatic and adipocyte lipogenesis, adipocyte maturation and adiponectin release

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