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ABC of obesity
Management: Part II—Drugs
Mike Lean, Nick Finer

Despite the availability of evaluated and approved obesity drugs—and even though some patients will have failed to lose weight after non-drug treatment—doctors have been reluctant to prescribe drugs. The reasons for this may include memories of the adverse events with amphetamine, and amphetamine-like drugs, and the serious complications from combining phentermine and fenfluramine. Current drugs recommended for treating obesity have all been evaluated and approved by regulatory standards that apply to all drug treatments. The use of obesity drugs should follow the principles of any other therapeutic area—that is, they may be prescribed after assessment of the potential benefits and risks (both clinical and economic), with appropriately informed patients, and with medical monitoring of the results of treatment.

Many people, including doctors, still believe that a short course of drug treatment might "cure" obesity or that efficacy is measured only by ever-continuing weight loss. These misconceptions are at odds with biology: people who become obese have a lifelong tendency both to defend their excess weight and to continue to gain extra body fat. Effective management, including drugs when needed, must be life long and focused on weight loss maintenance in a similar fashion to the effective treatment for hypertension or diabetes. Drug efficacy can be considered in terms of the impact on measures such as body mass index or fat distribution, risk factors, disease improvement, or reduction in clinical end points. Starting drug treatment should always be regarded as a therapeutic trial and stopped if weight loss is not apparent after one to two months.

Drug treatment of the consequences of obesity

Current approaches to obesity management largely involve trying to treat all the additional symptoms, risk factors for future disease, and existing comorbidity without necessarily tackling the primary problem. The excess polypharmacy administered to obese patients was highlighted in a recent audit of primary care (the UK Counterweight programme). Obese patients often take five or more different drugs, all for components of metabolic syndrome, plus symptomatic treatments such as use of bronchodilators, analgesics, and drugs for arthritis and angina. Insulin sensitising agents (such as metformin) are sometimes used to try to improve several obesity related risk factors simultaneously, but they rarely adequately improve the hazards and symptoms of obesity, so polypharmacy may still be necessary.

Treating obesity itself

If the many diseases associated with obesity are causally related, then they will be modified by treatments that can generate weight loss (that is, loss of body fat) and prevent the regain of excess body fat. Inherent in this is a need to establish energy balance at a lower body weight. Temporary weight loss by liposuction does not do this, nor does it affect metabolic risk.

An effective drug against obesity must reduce energy assimilation from food (without compensatory reduction in

Diet and exercise play a central role in preventing obesity and are the first line treatment for the condition. But many patients also need drugs to help them lose weight, and to maintain the loss, however that was achieved.

Clinical targets from which to evaluate drug efficacy in interventions for weight management

<table>
<thead>
<tr>
<th>Physical measure</th>
<th>Risk factor</th>
<th>Disease severity</th>
<th>Clinical end points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Changes in mass (body mass loss, maintenance of body mass loss, maintenance of fat loss, body mass index); changes in fat distribution (waist circumference, abdominal fat area,* visceral fat volume†)</td>
<td>High levels of fasting cholesterol and triglycerides; low levels of high density lipoprotein cholesterol; high blood pressure; left ventricular hypertrophy</td>
<td>Glycaemic control; quality of life; left ventricular function</td>
<td>Cardiovascular event; cardiovascular mortality; development of diabetes; unwanted effects; joint pain; sleep apnoea; depression</td>
</tr>
</tbody>
</table>

*Derived from computed tomography or magnetic resonance imaging †Predicted from cross sectional computed tomography, magnetic resonance imaging, or (more weakly) dual emission x ray absorptiometry (DEXA)—which measures the density of bones.

Obese patients are at increased risk from cardiovascular disease: it is imperative that risk factors are treated early and optimally. Effective treatment to prevent the underlying cause (body fat accumulation) would make better clinical and economic sense and is now accepted as a reasonable target for drug development.

Liposuction removes only subcutaneous fat, which carries little metabolic risk, and energy intake is unaffected; thus body weight will rise again to achieve energy balance.

This is the fourth article in the series.
energy expenditure) or stimulate energy expenditure (without compensatory increase in food consumption), or both. Current drugs act mainly on energy intake; for maximal effectiveness, they depend on patients adopting a well designed diet and lifestyle programme. In a recent one year study, intensive lifestyle intervention produced weight loss (6.7 (standard deviation 7.9) kg) similar to that achieved with the drug sibutramine alone (5.0 (7.4) kg); combining lifestyle intervention with the drug doubled the weight loss (12.1 (9.8) kg).

**Principles of drug therapy**

*Weight loss*—The benefit of obesity drugs depends on effects on body fat and body weight. Two thirds of patients can achieve a 5-10% loss in three to six months with lifestyle modification and drug treatment. A weight loss of less than 1-2 kg after six weeks indicates an inadequate response, except in patients who have already lost weight with diet and exercise and patients with type 2 diabetes.

*Weight maintenance*—Most patients who lose weight regain it. Drugs are a logical treatment not just for weight loss induction but for long term weight loss maintenance. A reasonable long term target is to restrict regain—for example, to below the average rate of weight gain (1-2 kg a year for obese people).

*Symptoms and risk factors*—Patients should show long term improvements as a consequence of the weight control or through separate mechanisms of the drug.

*Duration of treatment*—It is logical to continue the drug for as long as it is effective; if the drug is effective, withdrawal will lead to weight regain. Current licensing criteria still limit treatment duration to one to two years, although for some drugs, trials show continuing benefit. Treatment beyond this limit, however, must still be recognised as “off licence,” and patients should be counselled and supervised accordingly.

*Side effects and safety*—Overall risk to benefit of existing drugs has been favourably shown in terms of symptoms, risk factors, and diabetes prevention. As for any other disease, patients have to be seen regularly for benefit to be assessed and unwanted effects identified. Limited information on safety and efficacy exists for elderly people, children, and adolescents. Pregnant and breast feeding women should not take obesity drugs.

**Drugs licensed for obesity management**

**Orlistat**

Orlistat is an intestinal lipase inhibitor taken three times daily with meals. It generates malabsorption of 30% of dietary fat. It leads to 5-10% weight loss in 50-60% of patients, and in clinical trials the loss (and related clinical benefit) is largely maintained up to at least four years.

In a recent review by Finer et al (see Further Reading box), when orlistat was compared with placebo, all risk factors for coronary heart disease improved and 37% fewer patients (72% of those with impaired glucose tolerance) developed diabetes over four years. Reduced intestinal fat absorption may have direct effects on improving lipids and insulin sensitivity.

Outcome improved with a structured diet and exercise programme. (A good action plan (known as MAP) is provided, via the makers of orlistat, to patients prescribed the drug.) Patients who do not follow advice to eat a low fat diet (in general < 60 g fat a day) will have steatorrhoea. Gastrointestinal side effects are not necessary for effective weight loss because malabsorption of 20 g of fat is usually asymptomatic and produces an energy deficit of 180 kcal a day.

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**What current obesity drugs can do**

* Increase weight loss by about 4-6 kg beyond what can be achieved by diet alone
* Maintain weight loss (however achieved) 12-15 kg below baseline
* Improve most cardiovascular risks in direct relation to weight loss

**Combining drugs with different mechanisms is a logical way to increase efficacy. However, the limited evidence does not support combining orlistat and sibutramine**

Proportion of study participants achieving 5-10% weight loss in one year, according to drug taken (data from combined datasets of 1 year phase 3 trials of three obesity drugs including rimonabant (adapted from Finer N, see Further Reading box).
**Sibutramine**
Sibutramine inhibits the reuptake of noradrenaline and serotonin, promoting and prolonging satiety; it is taken once daily. It produces 5-10% weight loss in 60-70% of patients, and in clinical trials it is well maintained for at least two years. If weight loss is less than 2 kg at four weeks, the dose can be increased from 10 mg to 15 mg.

High density lipoprotein cholesterol concentrations increase by 25%, partly independently of weight loss. The noradrenergic action increases heart rate by 1-2 beats/min and attenuates the fall in blood pressure expected with weight loss. Some patients, especially if they fail to lose weight, may record a rise in their blood pressure; it is therefore essential to monitor blood pressure during the first 12 weeks of treatment. Controlled hypertension is not a contraindication for prescribing sibutramine.

**Rimonabant**
Rimonabant is the first cannabinoid-1 receptor antagonist to be licensed for obesity treatment. Stimulation of cannabinoid-1 receptors in the brain promotes eating and in peripheral tissues cardiovascular risk factors such as low concentration of high density lipoprotein cholesterol, insulin resistance, and inflammation. Blockade with rimonabant produces weight loss and weight-independent improvements of some cardiovascular risk factors.

Rimonabant produces 5-10% weight loss in 60-70% of subjects, maintained for up to two years in clinical trials. Side effects reported were mild and infrequent. Clinical trials excluded depressed patients; effects on mood and depression should be assessed during routine clinical care.

**The three licensed obesity drugs (orlistat, sibutramine, rimonabant) can all significantly improve glycaemic control in overweight patients with diabetes**

**Incidence of side effects expressed as ratio of active treatment to placebo from clinical trials of orlistat, sibutramine and rimonabant. Adapted from Greenway and Caruso (see Further Reading box)**

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Orlistat</th>
<th>Sibutramine</th>
<th>Rimonabant (20 mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dry mouth</td>
<td>-</td>
<td>4.1</td>
<td>-</td>
</tr>
<tr>
<td>Dizziness</td>
<td>1.0</td>
<td>2.4</td>
<td>1.8</td>
</tr>
<tr>
<td>Nausea</td>
<td>1.1</td>
<td>2.1</td>
<td>3.0</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>-</td>
<td>-</td>
<td>2.4</td>
</tr>
<tr>
<td>Constipation</td>
<td>-</td>
<td>1.9</td>
<td>-</td>
</tr>
<tr>
<td>Oily spotting*</td>
<td>20.5</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Flatus with discharge*</td>
<td>20.9</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Faecal urgency*</td>
<td>3.3</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Fatty or oily stool*</td>
<td>6.9</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Oily evacuation*</td>
<td>14.9</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Increased defecation*</td>
<td>2.0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Faecal incontinence*</td>
<td>8.6</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Musculoskeletal disorder</td>
<td>2.0</td>
<td>1.6</td>
<td>1.1</td>
</tr>
<tr>
<td>Anxiety</td>
<td>1.6</td>
<td>1.3</td>
<td>3.3</td>
</tr>
<tr>
<td>Depression</td>
<td>0</td>
<td>1.7</td>
<td>12.3</td>
</tr>
<tr>
<td>Insomnia</td>
<td>1.2</td>
<td>2.4</td>
<td></td>
</tr>
<tr>
<td>Cardiovascular disorder</td>
<td>1.0</td>
<td>2.2</td>
<td>0.8</td>
</tr>
<tr>
<td>Hypertension</td>
<td>-</td>
<td>2.3</td>
<td>-</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>-</td>
<td>4.3</td>
<td>-</td>
</tr>
<tr>
<td>Palpitation</td>
<td>-</td>
<td>2.5</td>
<td>-</td>
</tr>
</tbody>
</table>

Dashes indicate “not reported.”
*These effects occur only if excess fats are eaten.

**Sibutramine’s main side effects include a dry mouth, constipation, headaches, and dizziness; all may be improved by drinking more water when losing weight. Poor sleep and agitation may occur early in treatment and are usually self limiting. Several potential drug interactions (for example, with selective serotonin reuptake inhibitors) may limit usage**

**Drugs that are not recommended**
- Methyl cellulose is still licensed in the UK as an adjunct in obesity, but no evidence exists for its efficacy or safety
- Phentermine is a catecholamine releasing agent that stimulates the central nervous system, producing appetite suppression. Efficacy and safety have not been sufficiently established

**Drugs licensed for non-obesity indications**
- Any drug that produces anorexia or nausea as a side effect will produce weight loss but would be inappropriate as an obesity treatment.
- Metformin produces minor effects on body weight but improves insulin sensitivity, preventing progression from impaired glucose tolerance to diabetes. It improves fertility in women with polycystic ovarian syndrome. Gastrointestinal side effects, however, may limit its use.
- In epileptic patients, topiramate (atypical anticonvulsant) produces less weight gain than other anticonvulsants and often striking weight loss. It was withdrawn during clinical trials for use in obesity because of cognitive side effects at effective doses in non-epileptic subjects

**Weight loss over first year of treatment with rimonabant (combined with lifestyle modification) is maintained in year 2 if drug is continued. Weight regain occurs if drug is withdrawn even if lifestyle modification is continued** (adapted from Pi-Sunyer et al. JAMA 2006;295:761-75)
New drugs in development

Clinical trials are now well advanced for several drugs with different modes of action.

Many of the hormones and hormone receptors that contribute to regulation of appetite or satiety are targets for drug treatment and under active development in preclinical and early clinical trials. Newer agents primarily designed to treat diabetes, such as the synthetic amylin pramlintide and GLP-1 analogue exenatide, are licensed in the US and unlike most other hypoglycaemic drugs lead to clinically important weight loss.

For the very rare cases of leptin deficiency, daily injections are curative. Most obese people, however, have high concentrations of leptin, and trials of hyperaugmentation were disappointing. Rosenbaum et al found that after 10% weight loss induced by a low energy liquid diet, recombinant leptin restored circulating leptin concentrations, energy expenditure, the work efficiency of skeletal muscle, sympathetic nervous system tone, and circulating concentrations of thyroxine and triiodothyronine to levels present before the weight loss (Journal of Clinical Investigation 2005;115:3579-86).

Pharmacoeconomics

Drug treatment is considered effective (in terms of numbers needed to treat) and cost effective by the National Institute for Health and Clinical Excellence, with an overall cost per quality adjusted life year of £19 000 (€27 500; $35 000) to £55 000, which can be further improved by targeting patients with comorbidities.

Cost effectiveness is estimated to vary between €3462 per life year gained for obese diabetic patients with hypertension and hypercholesterolaemia and €19 986 per life year gained for obese diabetic patients without other risk factors (Diabetes Care 2002;25:303-8).

Evaluation of drug treatment in routine clinical practice, including cost effectiveness studies, is confounded when data from randomised controlled trials are used because patients who fail to respond to treatment continue to be included. In routine practice, such patients’ treatment would be stopped at an early stage. Long term randomised controlled trials of obesity drugs thus tend to exaggerate costs of effective treatment by about 20%.

Useful websites

- www.counterweight.org (multicentre obesity management project led by practice nurses, conducted in seven UK regions)
- www.changeforlifeonline.com (week by week plan for lifestyle changes for patients taking sibutramine)
- www.iswhatsyourgoal.co.uk (support site for patients taking rimonabant)
- www.rcplondon.ac.uk/pubs/wp_antiobesitydrugs.htm (Royal College of Physicians’ guidelines) (accessed 10 Jul 2006)
- www.nice.org.uk (National Institute for Health and Clinical Excellence is an independent organisation responsible for providing national guidance on promoting good health and preventing and treating ill health)
- www.cochrane.org (for Cochrane reviews)
- www.jr2.ox.ac.uk/bandolier/band100/b100-4.html (for research information on obesity drugs)
- www.obesity-news.com (for research information about obesity drugs)

Key references and further reading

- Curran MP, Scott LJ. Orlistat: a review of its use in the management of patients with obesity. Drugs 2004;64:2843-64.

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Competing interests: Nick Finer has received research grants and consultancy fees from, and served on advisory boards to, many pharmaceutical companies involved in the development of treatments for obesity and diabetes, including Roche, Abbott, Sanofi-Aventis, Merck, Shionogi, Pfizer and GlaxoSmithKline. For series editors’ competing interests, see the first article in this series.

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