Obesity is a serious chronic disease; no less a disease than the type 2 diabetes, osteoarthritis, and obstructive sleep apnoea that it drives. Weight loss is the most effective way to treat the host of medical and psychological conditions, physical disability, and impaired quality of life associated with overweight and obesity. However, powerful neuroendocrine mechanisms defend body weight and body fat stores making it extremely difficult to achieve and maintain substantial weight loss.1

Treating obesity is therefore challenging and requires regular commitment to the patient in a similar multifaceted way to that required to effectively manage patients with other chronic conditions. The general practitioner is ideally placed to provide and coordinate this long term care. Unfortunately, barriers including poor understanding of the pathophysiology of disease, perceived ineffectiveness of therapy, unrealistic expectations, and time constraints, have stood in the way of better medical care.

There is a strong evidence base supporting the effectiveness and benefits of weight loss and weight control measures. Modest weight loss has a disproportionate effect on many of the more serious obesity related comorbidities. Both Finnish and USA diabetes prevention trials indicate the profound effect of lifestyle measures in achieving modest weight loss (Table 1).

Once weight loss has been achieved, the problem of weight maintenance is the next significant hurdle. The US National Weight Control Registry provides details of those who successfully lose and sustain substantial weight loss. Registrants must have maintained a weight loss of at least 13.6 kg for 5 years. While a range of methods were used to achieve weight loss, several common behavioural characteristics for weight loss maintenance were apparent (Table 1).

The National Health and Medical Research Council clinical practice guidelines suggest a stepped approach to the management of overweight and obesity with only those of significant risk requiring more intensive therapies such as pharmacotherapy, very low calorie diets, and surgery.2
Who should be considered for pharmacotherapy?

Several factors influence the selection of patients for more intensive therapy. Body mass index (BMI = weight in kg/height in m²) provides a good measure of body fatness, but indication for more intensive therapy needs to be adjusted for risk, ethnicity and the presence of obesity related disease (Table 2). A BMI of 27 kg/m² provides a more realistic cut off for added risk between normal and overweight caucasians.  

Pharmacotherapy is one of a range of additional therapies that can provide supplementary benefit to lifestyle modification. Pharmacotherapy for overweight and obesity should be considered in those with a BMI >30 kg/m² and for those with a BMI 27–30 kg/m² with increased risk. This includes Asian ethnicity, or those with overweight/obesity related disease likely to improve with weight loss, such as type 2 diabetes, obstructive sleep apnoea and dyslipidaemia of obesity. For Asian populations, high risk BMI levels should be reduced by 2–3 BMI points.

There are few drugs currently approved for the treatment of obesity in the Australian population (Table 3).

Currently available medications

Sibutramine

This centrally acting noradrenaline serotonin uptake inhibitor suppresses appetite and, along with lifestyle modification, provides a mean weight loss of approximately 4.5 (CI: 3.6–5.3) kg at 1 year when compared with placebo. Following significant weight loss, sibutramine is more effective than placebo at preventing weight regain and intermittent use has also been proven effective. A program of sibutramine and lifestyle modification is considerably more successful than either therapy used alone. Common reported side effects are usually mild and transient, and include dry mouth, constipation, headaches, and insomnia. Sibutramine produces a dose related increase in heart rate and may increase blood pressure. It should be used with caution in hypertensive individuals and blood pressure should be monitored in all patients. Sibutramine is contraindicated in poorly controlled blood pressure, coronary artery disease, cardiac failure, arrhythmias, severe renal or liver dysfunction, anorexia and bulimia, and in patients using monoamine oxidase inhibitors. Its effectiveness and safety beyond 2 years of treatment are unknown.

Orlistat

Orlistat binds to intestinal and pancreatic lipases in the gut, preventing their action on their lipid targets. It reduces the absorption of dietary triglycerides, cholesterol, and fat soluble vitamins. Taken in a dose of 120 mg three times per day with meals, approximately 30% of oral fat intake is excreted in the stool. Mean weight loss at 1 year is approximately 2.9 kg (CI: 2.3–3.5) when compared with placebo, and weight loss has been shown to be effective up to 4 years. Orlistat leads to more favourable changes in total cholesterol, LDL cholesterol levels, free fatty acids, HbA1c and insulin sensitivity than those expected for weight loss alone. Side effects of orlistat are related to its action and include: fatty oily stools, faecal urgency, diarrhoea, flatulence, faecal incontinence, bloating, and abdominal pain. While these problems are minimised by a low fat diet, fat malabsorption does increase the risk of vitamin D, E and beta-carotene deficiency. Daily fat soluble vitamin supplementation is recommended and supplements should be taken between meals (2 hours before and after orlistat ingestion). Orlistat is now available on pharmacist recommendation (S3).
**Short acting compounds**

Two noradrenergic compounds are available to assist in short term (weeks) weight loss. Both drugs were introduced in the 1960s, and while they have been available for more than 30 years, safety and efficacy data are limited. With no significant studies for over 20 years, they have not had the scrutiny of sibutramine and orlistat and are approved for short term use only.

**Phentermine**

Phentermine is an amphetamine-like compound that increases the release of noradrenaline and dopamine from nerve terminals, reducing appetite and increasing satiety. When used with lifestyle modification 15–30 mg of phentermine produces an average of 3.6 kg (CI: 0.6–6.0) greater weight loss than placebo. The longest study of 36 weeks duration demonstrated that continuous use and intermittent use (4 weeks on and 4 weeks off) provided similar benefit. While it is generally well tolerated, stimulatory effects of agitation and insomnia are the most common reason for therapy cessation. Usual side effects are related to its sympathomimetic amphetamine-like action and include dry mouth, insomnia, agitation, constipation, tachycardia, and elevated blood pressure.

**Diethylpropion**

A dose of 75 mg diethylpropion, when combined with lifestyle intervention, leads to a modest weight loss of 3.0 kg (-1.6–11.0) kg, which is of borderline statistical significance when compared to placebo. It is used either as a 25 mg dose 1 hour before a meal or as a single 75 mg extended release tablet. Data concerning any long term benefit are absent, and a somewhat rapid tolerance to the anorexic effects has been observed. Common side effects are sympathomimetic amphetamine-like with central nervous system stimulation, headache, insomnia, restlessness, palpitations, and an increase in blood pressure.

Contraindications to these noradrenergic agents include: anorexia, insomnia, psychopathic personality disorders, suicidal tendencies, Gilles de la Tourette syndrome and other disorders, hyperthyroidism, narrow angle glaucoma, diabetes mellitus, ischaemic heart disease, hypertension and arrhythmias. The real value of these medications in the long term management of obesity is unknown.

**Other medications**

Several drugs used for other indications can promote weight loss. One of the most promising compounds for the treatment of obesity was the anti-epileptic agent topiramate, however central nervous system side effects have precluded its use as a weight loss medication. Bupropion, introduced as a short term aid to smoking cessation, produces modest weight loss of 2.8 kg (CI: 1.1–4.5). When introduced into Australia there was concern regarding an apparent high rate of adverse neurological, psychiatric, and gastrointestinal events. Two selective serotonin reuptake inhibitor (SSRI) antidepressant medications, fluoxetine and sertraline (with similar actions to sibutramine), appear to have some weight loss properties. Formal studies of fluoxetine are mixed but promising for those with type 2 diabetes. There are no high quality studies involving sertraline.

**The future**

Rimonabant is the first endocannabinoid-CB(1) blocking drug. It appears to have both central and peripheral actions to reduce weight and weight related metabolic factors.

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**Table 2. Therapeutic options for weight loss**

<table>
<thead>
<tr>
<th>WHO description – BMI</th>
<th>Therapy*</th>
<th>Therapy if additional risk (ethnicity and related comorbidity)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal 20–25 (27)</td>
<td>Healthy lifestyle advice – dietary, physical activity and behavioural (no weight loss therapy indicated)</td>
<td>Healthy lifestyle advice</td>
</tr>
<tr>
<td></td>
<td>Low calorie diets</td>
<td>Healthy lifestyle advice if weight loss considered beneficial</td>
</tr>
<tr>
<td>Overweight 25 (27)–30</td>
<td>Healthy lifestyle advice</td>
<td>Healthy lifestyle advice</td>
</tr>
<tr>
<td></td>
<td>Pharmacotherapy, very low calorie diets</td>
<td>Healthy lifestyle advice</td>
</tr>
<tr>
<td>Class I 30–35</td>
<td>Healthy lifestyle advice</td>
<td>Healthy lifestyle advice</td>
</tr>
<tr>
<td></td>
<td>Pharmacotherapy, very low calorie diets</td>
<td>Healthy lifestyle advice</td>
</tr>
<tr>
<td>Class II 35–40</td>
<td>Healthy lifestyle advice</td>
<td>Healthy lifestyle advice</td>
</tr>
<tr>
<td></td>
<td>? Surgery</td>
<td>Healthy lifestyle advice</td>
</tr>
<tr>
<td>Class III 40+</td>
<td>Healthy lifestyle advice</td>
<td>Healthy lifestyle advice</td>
</tr>
<tr>
<td></td>
<td>Surgery (see the article by Brown et al this issue)</td>
<td>Surgery</td>
</tr>
</tbody>
</table>

*All therapy is additive with healthy lifestyle advice regarding behavioural, dietary and physical activity change; the cornerstone of therapy for all
such as increasing adiponectin and reducing circulating free fatty acids. Mean weight loss reported in the RIO-North America study\(^6\) was 4.7 kg at 1 year. Those who continued rimonabant during a second year retained their weight loss, while those who stopped regained weight. The study experienced a high dropout rate of almost half the participants by 1 year. The RIO-Europe study\(^7\) reported weight loss at 1 year of 1.6 kg and 4.8 kg for doses of 5 mg and 20 mg respectively when compared with placebo. Rimonabant appears to be generally well tolerated with primary side effects of nausea, diarrhoea, anxiety and depression.

While the number of weight loss medications is small, and the effects they provide modest, the future is promising. There has been an increase in our understanding of neuro-hormonal control of energy balance, fat as an endocrine organ, gut hormones and thermogenesis. These factors provide a range of targets where intervention may lead to significant weight loss or alleviation of the metabolic effects of excessive weight. As with other chronic disease, continuous combination drug therapy may be necessary for long term weight control.

**Conclusion**

Currently available pharmacotherapy provides modest weight loss if the therapy is continued. It is important that weight loss medications are prescribed in combination with, rather than in lieu of, lifestyle modification.\(^8\)

Conflict of interest: none declared.

**References**


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**Table 3. Weight loss medication currently available in Australia**

<table>
<thead>
<tr>
<th>Generic name</th>
<th>Trade name</th>
<th>Action</th>
<th>Usual daily dosage</th>
<th>Availability</th>
<th>Suitable duration</th>
<th>Cost per month (approximately)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anorexiant</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sibutramine</td>
<td>Reductil</td>
<td>Noradrenaline and SSRI</td>
<td>10–20 mg/day</td>
<td>S4</td>
<td>Long term</td>
<td>$111.00</td>
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<tr>
<td>Diethylpropion</td>
<td>Tenuate</td>
<td>Sympathomimetic</td>
<td>75 mg/day</td>
<td>S4</td>
<td>Short term</td>
<td>$32.00</td>
</tr>
<tr>
<td>Phentermine</td>
<td>Duramine</td>
<td>Sympathomimetic</td>
<td>30–40 mg/day</td>
<td>S4</td>
<td>Short term</td>
<td>$80.00</td>
</tr>
<tr>
<td><strong>Block fat absorption</strong></td>
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<tr>
<td>Orlistat</td>
<td>Xenical</td>
<td>Lipase inhibitor</td>
<td>360 mg/day</td>
<td>S3</td>
<td>Long term</td>
<td>$120.00</td>
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