

## Medical Management of Obesity and its Complications

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### Abstract

**Obesity is increasing and with this comes an increase in Metabolic Disease. Current therapies are effective. We need to establish groups that are experts in “lifestyle therapy” but make sure that they use the very effective adjunctive therapies when indicated. Whilst bariatric surgery is effective for those with Grade III obesity, it is important to realise that medical therapy is very effective for those who are overweight or with lesser degrees of adiposity. There needs to be a proper lifestyle programme and the use of adjunctive treatment when necessary. This approach can reduce weight, reduce cardiovascular risk, help control diabetes and prevent it. We MUST establish proper treatment programmes and follow-up systems.**

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### Introduction

Overweight and obesity are common in many countries throughout the world, and their prevalence is increasing not just in developed countries but also in developing countries as they become more affluent. While there is some discussion about whether obesity prevalence is increasing at as fast a rate, the fact remains that prevalence is high and increasing. With increasing obesity prevalence comes increasing obesity-associated disease. This is basically of 2 types; metabolic [type 2 diabetes mellitus (T2DM), hypertension, dyslipidaemia and consequent heart disease]<sup>1</sup> and mechanical (obstructive sleep apnoea, osteoarthritis).<sup>2</sup> Both major groupings of disease are improved by weight loss and proper management of weight and therefore it is necessary to understand modern management.

Particularly for metabolic disease, it appears to be the site, not just the amount of adiposity that it is important.<sup>3-5</sup> Therefore, it is necessary to recognise those with abdominal adiposity early and to intervene. Secondly, there is still some discussion about the appropriate “cut-points” for body mass index (BMI) and waist circumference in Asian populations. There is debate about whether these should be lower.<sup>6</sup> Some countries such as Japan and the People’s Republic of China have accepted lower action points. This article will not debate these issues, but will try and

present a rational, evidence-based approach to obesity management.

### Assessment of the Need to Manage Weight

There is some controversy surrounding the levels of adiposity at which one should intervene and what degree of medical management is required. It is simplest to make decisions after considering 3 measurements: height, weight and waist, and the consideration of how many risks or complications the patient has. The BMI and waist measurements are easy measures and are important. Greater abdominal adiposity, as assessed by waist, is associated with greater cardiometabolic risk.

The risks that should be considered are the presence of hypertension, impaired glucose tolerance or diabetes, dyslipidaemia, cardiovascular disease and obstructive sleep apnoea. The exact BMI cut-points and waist measures for various groups and countries are still being debated but there is a broad consensus (Table 1) and the assessment of obesity management can be based on these.

### Grade 1-Recognition Stage

BMI in the overweight (pre-obese) or at risk range of low waist and no complications: there should be recognition of potential problems and advice needs to be given on eating, exercise and lifestyle change to reduce adiposity to the

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normal range or at least prevent further weight gain. This programme need not be intense but should be advocated even if the patient is not overtly obese. As health professionals, we need to recognise and be prepared to broach the issue of being overweight earlier and to offer some help.

#### *Grade 2-Intervention Stage*

With BMI in the greater risk range (30 to 35 kg/m<sup>2</sup> in Europids or >27 in Europids if complications or high waist are present. In Asia the values would be BMI >27.5, or >25 and <30 if high waist or complications are present. As well, this group would contain those at high risk of developing diabetes. In this group, medical intervention with a lifestyle programme coupled where necessary with adjunctive therapy (see below) will reduce weight, reduce risk and prevent future disease such as diabetes.

#### *Grade 3-Major sustained intervention*

This group has BMI >35 in Europids with high waist and complications present, and in Asia, this refers to those with BMI >30 with high waist and complications. They require an intervention that is more aggressive and will usually commence with adjunctive treatment in addition to a structured intense lifestyle programme.

It must be emphasised that as one goes from overweight with no disease, to the need to prevent disease, to the presence of disease, the intensity of the intervention required is greater.

### **Goals of Medical Management**

These need to be set at the beginning of the intervention. They will vary with the individual and will include the patient's goals and also that of the health professionals. They will include prevention and control of metabolic disease, reduction in medications, ability to have a joint replacement or a very specific individual goal such as the ability to travel comfortably and safely.

Goals should be discussed, set and recorded and as the patient achieves a goal, this significant milestone should be noted and possibly rewarded.

### **The Medical Management of Obesity**

Despite difficulties in understanding (and the triteness of the nomenclature) a lifestyle programme is the basis of obesity management. Such a programme has the components of eating, activity, behaviour modification, psychological support, proper medical management of associated conditions and long-term follow-up. These have been shown to be effective, and a weight loss of 6% or more of initial body weight can be maintained.<sup>7,8</sup> Other studies suggest that weight losses greater than this can be achieved and maintained.<sup>9</sup> While the components of such a

programme cannot be discussed in detail in an article of this length, they will be considered. Beyond these basic interventions, the medical management of obesity includes the use of adjunctive therapy. This is specific pharmacotherapy for obesity,<sup>10</sup> the use of very low calorie diets (VLCDs)<sup>11</sup> and the newer mechanical devices such as intra-gastric balloons. Bariatric surgery is obviously effective,<sup>12</sup> but should still be reserved for the "upper end" of the obesity spectrum (BMI >35 with complications) to make the most effective use of such expensive resources.

### **Specific Lifestyle Programme**

Each programme for the management of obesity must be based around a lifestyle programme.

#### *Eating*

A great deal has been written about diets, advocating specific food types or regimes. There is a large diet industry. However it is important to eat less, therefore the diet should be mildly hypocaloric based on the individual's size. An energy deficit of 500 to 600 kcals seems to be accepted and tolerated by most patients. The prescribed diet (or preferably eating plan) should start from the patient's habitual macronutrient intake and make small changes. Compliance is more important than the type of diet. Some changes that can be recommended are less total fat and less saturated fat, possibly an increase in mono-unsaturated fats and lower glycaemic index carbohydrate.<sup>13</sup> There have been recent suggestions that an increase in protein intake may help weight loss, and the "protein leverage hypothesis" is being tested in a number of studies around the world.

#### *Activity*

This is also a major part of the programme. Activity helps maintain lean mass and promotes weight and fat loss (because it adds to the energy deficit). However, the type of exercise/activity done may vary, but it is necessary to be active every day. A way of assessing initially is to use a Physical Activity questionnaire, ask how many minutes of walking a day is done, and perhaps to use a pedometer to see what baseline activity really is. For those over the age of 40 with the co-morbidities of obesity and heart disease, a formal exercise assessment is recommended. From this baseline information, an exercise/activity programme can be prescribed. Patients actually comply better if the programme is formally prescribed by a medical practitioner.<sup>14</sup> Whilst walking is a usual activity prescribed, it is important to realise that variety in exercise is important and that the exercise chosen is one with which the patient is happy and can comply. The use of the combination of resistance and aerobic exercise supervised by an exercise physiologist can be of particular benefit in obese patients with diabetes and other metabolic disease. In our "Metabolic

Rehabilitation Clinic” at Concord Hospital, we require the patients attend 3 supervised sessions a week in addition to walking in their own time. This has proved most effective. Similarly, for diabetes prevention, supervised sessions have been a part of all effective programmes and as such should be part of any diabetes prevention programme.

Whilst a simple way of getting patients to be more active is to use a “Steps” programme it is important to remember 2 things. Firstly, the lower the patient’s weight, the greater the number of steps they have to do to achieve weight loss. Secondly, it is better as a practitioner to consider “volume of exercise” done (that is duration x distance x effort) as this gives a better guide to the amount of activity. Activity should be monitored formally (as in supervised sessions) or with logs kept by the patient. Increased activity alone, without a reduction in calorie intake, does not produce a great deal of weight loss although it may effect fat distribution with a reduction in abdominal fat which is desirable.<sup>15,16</sup>

**Behaviour Modification**

Together with the changes in eating and activity, it is important to look at changing behaviour and habits. There are a range of techniques which are beyond the scope of this article to review.<sup>17</sup> However, the keeping of logs (food, activity, mood) are useful, the technique of cognitive restructuring, psychological support and where necessary, counselling are all parts of good programmes. We have found cognitive behaviour therapy helpful, particularly in

optimising weight maintenance.

A good lifestyle programme will combine these elements, will see the patients on a regular basis and will try at each visit to introduce additional small changes to optimise weight loss. Such programmes can induce and maintain a 5% to 7% loss of body weight, provided there is continuing follow-up. In many programmes in the second year, weight regain does occur but weight remains below the starting weight in the programme.

If this programme is not successful or if goals are not attained or associated disease controlled (or eliminated), then adjunctive therapy should be considered.

**Adjunctive Therapy**

This article will not consider bariatric surgery as it is focussing on the medical management of obesity. However for those with Grade 3 obesity with co-morbidities, after an initial lifestyle programme, bariatric surgery should be considered. The good programmes are successful, producing 30% to 50% of excess weight loss together with improvement in co-morbidities.<sup>18,19</sup>

Adjunctive therapy should be considered when there is not adequate weight loss after 12 weeks of a lifestyle programme or if the patient has several co-morbidities which would benefit from extra weight loss. For an approach of the use of adjunctive therapy, see Kopelman and Caterson.<sup>20</sup>

There are several types of adjunctive medical therapies available. These are pharmacotherapy, very low energy diets (VLEDs)/meal replacements and devices (Table 2). It should be remembered that they often are used in combination (e.g. VLEDs and devices) or sequentially (e.g. VLEDs followed by pharmacotherapy).

*Pharmacotherapy*

Currently there are several classes of drugs available to help weight loss (Table 2). Not all drugs are available in all countries. The available drugs can be divided into centrally acting (phentermine and sibutramine) and peripherally acting (orlistat). One way of looking at these is the drugs approved for long-term use (sibutramine and orlistat) and those for short-term use (these tend to be older medications). All these drugs are active and can produce weight loss, but are more effective when used in combination with a formal, effective lifestyle programme.<sup>8</sup>

Phentermine is an older adrenergic agent (and one of a group of such agents including benzphetamine, diethylpropion and phedimetrazine). It is orally active, acts centrally and delays meal eating or produces early satiety. As it is an old drug, its initial trials were of short duration. One of the longest was of 39 weeks’ duration and both continuous or intermittent use of phentermine produced

Table 1. Suggested Assessment of the Need for Medical Management

	BMI	Waist	Complications present	Management
European	25-30	low	no	R
Asia	23-27.5	low	no	R
European	27-35	high	yes/no	I
Asia	25-30	high	yes/no	I
European	>35	high	yes	M
Asia	>30	high	yes	M

BMI: body mass index

High waist

European males >102 cm, females >88 cm

Asia males >85 cm, females >80 cm\*

\* This may vary from country to country and the values are those suggested by the Obesity in Asia Collaboration<sup>3-5</sup>

Management

R = recognition and institution of a supervised lifestyle programme (the emphasis may be on diet or exercise depending on the individual). There should be follow-up

I = structured more intensive intervention which may include adjunctive therapy

M = intensive medical management programme with adjunctive therapy considered early.

Table 2. Obesity Pharmacotherapy\*

Drug	Term of use	Dose
<b>Centrally Acting Drugs</b>		
<u>Adrenergic agonists</u>		
Phentermine	Short	15 to 45 mg/day
Diethylpropion	Short	25 mg tds
Mazindol	Short	
<u>Combined serotonergic/adrenergic agonist</u>		
Sibutramine†	Long	10-15 mg/day
<u>Altering absorption</u>		
Orlistat	Long	180-300 mg/day
Other drugs not approved for use		
<b>Centrally Acting</b>		
<u>Adrenergic agonist</u>		
Ephedrine/Caffeine‡		
<u>Serotonin Agonist</u>		
Fluoxetine		
<u>Other action</u>		
Topiramate		
<b>Altering absorption</b>		
Acarbose		
<b>Other action</b>		
Metformin		

\* this table is not exhaustive including all possible drugs

† also has a peripheral action as a selective norepinephrine reuptake inhibitor (SNRI) as well as its central action as a SSRI

‡ available in Denmark

more weight loss than placebo.<sup>21</sup> In our own work in a 6-month trial with follow-up, it was far more effective than placebo producing initial weight loss which was then maintained over the period of follow-up (personal communication). Its side-effects include insomnia, dry mouth, constipation and asthenia.

*Siburamine* is both a selective serotonin reuptake inhibitor (SSRI) and a norepinephrine reuptake inhibitor (SNRI). It has been shown to be more effective than a lifestyle programme alone, with approximately two thirds of patients losing >5% of their weight and one third lost >10% on a 10 mg dose.<sup>22</sup> The longest reported trial is the Sibutramine Trial of Obesity Reduction and Maintenance (STORM).<sup>23</sup> This trial had an open label 6 months of treatment with 10mg sibutramine. Those who had lost 8kg or more were randomised to placebo/lifestyle treatment for 18 months whilst others were continued on sibutramine. There was weight regain in those on placebo, but those on sibutramine maintained weight for 12 months. In this trial, it was noticed that there was an increase in HDL cholesterol in those treated with sibutramine, an increase of some 21% in those on sibutramine for 2 years and a lesser increase in those who were switched to placebo. Sibutramine has also

been trialled as intermittent therapy for 52 weeks and this approach also produced significant weight loss.<sup>24</sup>

Concerns have been expressed about possible hypertension and slight increase in pulse that sibutramine can produce.<sup>25</sup> More recent post-marketing studies and a report from the early stages of the Sibutramine Cardiovascular Outcomes Trial (SCOUT) suggest that those with hypertension get a fall in BP when treated with sibutramine, although there is still a slight increase in pulse rate.<sup>26,27</sup> This may be due to the central alpha (clonidine-like) effect of sibutramine.<sup>28</sup>

With weight loss with sibutramine, there is a fall in blood glucose and an improvement in diabetic control in diabetic patients,<sup>29</sup> and triglycerides fall. These changes are consistent with the weight loss obtained. It appears that those with diabetes do not lose weight as well as those without.

*Rimonabant* is a new drug acting on the endocannabinoid system. It is a specific blocker of CB-1 receptors. It has central effects on appetite and eating and peripheral effects on fat cells explaining some of its effect in improving insulin sensitivity. It appears to reduce food intake and possibly increases energy intake in humans.

Four major trials<sup>30-33</sup> of its effect on weight, diabetes and risk factors have been reported. In essence, rimonabant (20 mg) resulted in weight reduction, and this is mirrored by waist circumference reduction correspondingly. The studies are consistent and as with sibutramine, if patients cease the drug and are switched to placebo, weight gain ensues. With rimonabant, there are increases in HDL cholesterol, a fall in triglycerides and improved diabetes control. It is argued that there may be a direct effect on adipocytes with an increase in adiponectin and a greater fall in glycated haemoglobin than would be expected from weight loss alone. Again those with diabetes did not get as great a weight loss. There is a fall in BP, but the studies are not consistent. Those with metabolic syndrome improved.

Side-effects of rimonabant include nausea and vomiting, diarrhoea, headache, dizziness, mood changes and anxiety. These latter effects were increased in the first year of treatment. Though not all the studies showed increases in depression or anxiety, it should not be used in patients with depression as it has not been studied in such patients.

However as of November 2008, rimonabant has been withdrawn in Europe and other countries as it was felt that because of its psychiatric side effect profile there was not enough benefit with the weight loss obtained. Whilst this drug class is of interest it is no longer a therapeutic option.

Orlistat acts peripherally. It is an inhibitor of gastric and intestinal lipases and this results in up to 30% of ingested fat being not absorbed. It must be used with a low fat diet

to minimise the side-effects of diarrhoea and fat leakage. It is an effective drug, producing an additional 70% weight loss over a lifestyle programme plus placebo (10.2% of initial body weight vs 6.1% with placebo).<sup>34</sup> There have been quite a number of trials, for up to 4 years, demonstrating its effectiveness.<sup>35-39</sup> It produces weight and waist loss, reducing LDL-cholesterol and triglycerides. There is an increase in HDL cholesterol. These effects continue for up to 4 years and the weight loss maintained on Xenical (some 6.7 kg) prevented up to 80% of diabetes incidence compared to the reduction in incidence in other diabetes prevention programmes (about 58%) which use lifestyle interventions alone. Orlistat is effective in those with type 2 diabetes,<sup>39,40</sup> producing weight loss and better diabetes control. In part this may be due to less insulin resistance because of the absorption of less fat.<sup>41</sup>

The usual dose of orlistat is 60mg or 120mg with meals. Orlistat is not absorbed and is a safe drug. Its side-effects relate to the fat malabsorption it produces. Diarrhoea and faecal fat loss are common initially, though reduced by a low fat diet and settle with time. They may also be used as a “learning experience” – “if you got side-effects think of the foods you ate, they must be higher in fat than you realise”. No problems have been shown with fat-soluble vitamins. However for long-term use, a vitamin supplement, given at night, could be recommended.

A new drug in this class, certilistat, is being trialled. It is said to produce less gastrointestinal side-effects. Weight loss with this drug is similar.<sup>42</sup>

Other drugs which have been shown to produce weight loss include the anti-epileptic drugs topiramate,<sup>43</sup> zonisamide and lamotrigine. Metformin seems to permit weight loss in those with diabetes, or to prevent diabetes in those at risk.<sup>21,44,45</sup> Other drugs such as the GLP-1 agonists (exenatide is an example) and amylin analogues (e.g. pramlintide) are being studied for their potential and role in obesity treatment.

The choice of drug to use depends on the clinical situation. As a broad rule of thumb, for those who are restricting their eating, have episodes of emotional eating or binges, or are getting hungry, sibutramine may be the drug to use initially. When people, usually men, have little experience with dieting or in those with diabetes, orlistat may be the drug used. There are clear guidelines for responders who lose weight well in the first 6 weeks to 3 months. The length of treatment is variable. Some patients may reach their goal relatively quickly, then the drug may be ceased but if there is a degree of weight regain (e.g. 4 kg) a second course may be initiated. Others may need to be on therapy for longer (the reported experience is 2 to 4 years), but when they cease therapy if there is a predetermined amount of weight regain, then pharmacotherapy should be reinstated.

*Combination therapy* has been studied in some small trials. There was no additional weight loss.<sup>46</sup> This may be because the mechanisms of action (reduction in intake and faecal loss) to a certain extent cancel one another out. Other combinations are under development (phentermine with topiramate, naltrexone with bupropion).

*Drug therapy in children and adolescents* with sibutramine and orlistat has been studied.<sup>47,48</sup> Both are effective and are used in adolescents, although generally in those who are larger or with significant complications. The duration of therapy is uncertain and each case should be decided on individual merits and closely monitored.

#### *Very Low Energy Diets (VLEDs) or Meal Replacements*

These are effective. There are a number of formulations available and come as shakes, soups or bars. They reduce energy intake (if on a full meal replacement protocol this can be 500 to 800 kcal/day) whilst providing necessary vitamins and micronutrients. The formulations provided by reputable nutrition or ethical pharmaceutical companies do provide good quality protein. For a practical review of their use, see Franklin and Summerbell.<sup>49</sup>

They may be used as a full replacement programme and if used as such, patients should be monitored regularly and be given a protocol. They produce a good initial weight loss and are generally used for 12 to 16 weeks before patients are switched to a normal lifestyle programme. In early results we found that at the end of 12 months, the weight loss was similar whether patients had been on a lifestyle programme alone or initially on VLEDs<sup>11</sup> but results have improved. A full meal replacement regime with VLEDs has been used as a “control” medical treatment arm in a study of the results of bariatric surgery where a reasonable weight loss ensured.<sup>50</sup> Other studies have shown that 1 or 2 meal replacements a day can produce significant weight loss which can be maintained for years.<sup>51</sup> This approach is useful, especially in those in the lower BMI range who need to lose weight and maintain it. There is no reason not to use meal replacements (1 or 2 per day) long term to maintain weight loss.

#### *The Future*

Whilst weight loss does reduce cardiovascular risk and improve diabetes control, intentional weight loss has still to be shown to reduce mortality. Several trials are underway and the results are expected in the next few years.

#### **Summary**

For those with a BMI between 27 and 35, especially those with metabolic complications, medical therapy is effective. A comprehensive lifestyle based weight loss programme plus the use of adjunctive therapy can initiate and maintain weight loss. The use of adjunctive therapy enhances and

maintains these results. We need to establish the type of clinics and programmes that will utilise and demonstrate the effectiveness of the therapy available.

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