Medicines for weight loss – do they work?

Key concepts

- Improving diet and increasing physical activity are the main strategies for weight loss
- Weight loss medicines may be considered for some people who have not attained a healthy weight with lifestyle changes alone, especially if they still have central obesity related risk factors
- Treatment with a weight loss medicine is only an adjunct to lifestyle change which must be maintained during and after treatment
- Medicines only produce modest reductions in weight but this may be sufficient for health benefits such as reduced cardiovascular risk
- People are likely to regain weight when medicines are stopped and there is no strong evidence that medicines are effective long-term

Improving diet and increasing physical activity are the main strategies for weight loss

Healthcare professionals want patients to lose weight to improve their metabolic problems and reduce cardiovascular (CVD) risk. Patients often want to lose weight so they can be more socially and physically comfortable. Both reasons are valid, and the decision on how to achieve the weight loss should be worked out between healthcare provider and patient.

Lifestyle changes, primarily based on improvements to diet and increased physical activity, are the mainstay of weight loss. Dietary changes may involve either a reduction in total energy intake (e.g. decreasing consumption of energy rich foods) or modifying the types of food in the diet (e.g. reducing the fat or refined carbohydrate content of the diet or increasing the protein content).[1] These changes, along with increasing fruit and vegetable intake are far more likely to reduce the risk of type 2 diabetes and CVD than weight loss alone.[2]

Increased physical activity involves undertaking moderate intensity exercise, such as brisk walking, for 30 minutes, five or more days a week.

Target weight loss is individual however, a reduction of 5 – 10 % of original body weight is realistic. Patients should usually aim to achieve a modest weekly weight loss (e.g. 0.5 – 1 kg) although weekly weighing is often unreliable and may be distressing.[3, 4, 5] A waist measurement reduction of 5 – 10% can be a more accurate predictor of health gains as intra-abdominal fat is often lost early, especially with exercise. With increased physical activity, some people gain weight through increased muscle mass, yet they still lose the important fat around the waist and reduce their waist measurement.

There are two main types of obesity

Obesity may be categorised as two different types:

- **Peripheral obesity** characterised by "below the waist" hip and thigh fat which is often difficult to lose and is more common in women. Weight loss medicines have limited usefulness for this type of obesity.
- **Central obesity** associated with hypertension, dyslipidaemia, type 2 diabetes, CVD, sleep apnoea, osteoarthritis, fatty liver disease and some cancers.[3] Weight loss medicines including metformin may be useful for some people in conjunction with overall lifestyle changes.

Body mass index and waist circumference

Body mass index (BMI) is a common way of assessing obesity in populations. It is calculated as body weight (in kg) divided by height (in metres) squared. Body composition between people with the same BMI can be variable. BMI is not always reliable in very old and very young people, those with a greater muscle mass or for ethnic groups with a smaller stature (e.g. South East Asians).[3, 6]

Abdominal circumference is a practical measure of abdominal fat and metabolic risk. Intra-abdominal fat, or visceral fat, is associated with an increased risk of conditions such as type 2 diabetes and CVD.[3] Risk is increased with a waist circumference greater than 88 cm in women and 102 cm in men.

Weight loss medicines may be considered for those who have not achieved a healthy weight with lifestyle changes alone

Pharmacological treatment of weight loss may be appropriate as an adjunct to lifestyle interventions for some people. A weight-loss medicine may be added to a regimen of dietary modification and increased exercise for people who have not reached a healthy weight, still have central obesity related CVD risk factors or have reached a plateau with diet and exercise alone.

Generally the criteria for considering medicines for weight loss are a BMI above 30 or a BMI above 27 in the presence of coexisting conditions such as diabetes, dyslipidaemia, hypertension or sleep apnoea.[3] For people with a BMI above 40 or above 35 with risk factors, surgical intervention may be a more appropriate option than weight loss medicines.

Orlistat

Orlistat (Xenical) is a lipase inhibitor that reduces dietary fat absorption by about 30%. Dietary fat is prevented from being broken down and digested and faecal fat is increased.[3, 7] It is important to note that any diet involving a reduction in total energy is associated with weight loss, not just a low fat diet.

In one meta-analysis, patients in the orlistat group lost on average 2.9 kg more weight than those in the placebo group, and 12% more patients taking orlistat achieved greater than 10% weight loss compared to placebo.[8] In both the orlistat group and the placebo group patients were encouraged to eat a low fat diet and to exercise. This translates into a number needed to treat (NNT) of eight which means that eight patients would need to be treated with orlistat for one patient to lose at least 10% of their body weight.[8]

In the same meta-analysis and in one local study,[9] significant reductions were seen in some secondary end points such as total cholesterol, LDL cholesterol, blood pressure and fasting plasma glucose.

Gastrointestinal adverse effects, relating to orlistat's mechanism of action, are common and experienced by about one in four people.[4] These include fatty/oily stools, faecal urgency, oily spotting and flatus with discharge. These adverse effects are typically short-lived as patients learn to avoid high fat diets to minimise these effects. Some patients may find it difficult to manage the three times per day regimen and adverse effect profile.

Patients taking orlistat may require supplementation with fat soluble vitamins (vitamins A, D, E, K and beta Carotene) because a long term decrease in fat absorption may result in a decrease in their levels.[6]

Orlistat is not subsidised. It may be obtained on prescription or as an over-the-counter medicine from pharmacies. The approximate cost to the patient for one month's supply is $164.

Sibutramine

Sibutramine (Reductil) suppresses appetite and increases energy expenditure by inhibiting serotonin and noradrenaline reuptake.[3, 10]

Sibutramine has recently been withdrawn from European markets. The Sibutramine Cardiovascular OUTcomes (SCOUT) trial showed a 16% rise in the risk of serious, non-fatal cardiovascular events, such as stroke or myocardial infarction in people using sibutramine. In New Zealand, Medsafe has stated that it is now reviewing the balance of risks and benefits of using Sibutramine.[11, 12]

For further information see BPJ 26 (Mar, 2010) "Sibutramine withdrawn from European markets".

People taking sibutramine lose on average 4 kg more weight over one year, and an additional 18 to 25% achieve greater than 10% weight loss at one year, compared with placebo (diet and exercise alone, NNT = 6).[8, 13] Sibutramine is associated with significant reductions in triglyceride concentrations and increased concentrations of HDL cholesterol.[4]

Sibutramine is contraindicated in patients with inadequately controlled hypertension, coronary artery disease, congestive heart failure, tachycardia, peripheral arterial occlusive disease, arrhythmia or stroke. Adverse effects reported by patients include insomnia, nausea, dry mouth, constipation and anxiety. Other potentially more serious adverse effects include an increase in heart rate and blood pressure.[4]

For the first three months, blood pressure and pulse rate should be measured fortnightly. Treatment should be discontinued in patients who, at two consecutive visits, have an increase in resting heart rate of greater than 10 bpm or systolic/diastolic blood pressure of greater than 10 mm Hg.[14]

Sibutramine is available on prescription only and is not subsidised. The approximate cost to the patient for one month's supply is $70.

Phentermine

Phentermine (Duromine) is an adrenergic stimulant, derived from amphetamine, that stimulates the release of noradrenaline and reduces food intake.[10]

There is limited data on the long term effectiveness of phentermine, although it has been in widespread use for 40 years. The New Zealand guideline for weight management did not find any evidence to assess the one year effect of phentermine and it was not considered an option for long term management of weight loss.[3]

Compared to amphetamine, phentermine has a much lesser effect on dopamine release. In people who do not abuse drugs, it is not stimulating or habituating, as evidenced by its continued availability. Phentermine is a controlled drug in New Zealand and is contra-indicated in people with a history of drug or alcohol abuse.[15]

Weight loss medicines – use and interactions

Medicine	Directions for use	Interactions
Orlistat	120 mg three times a day with each main meal. The dose can be omitted if a meal is missed, or if the meal contains little or no fat.	Orlistat may alter the anticoagulant effect of warfarin; INR should be monitored. Orlistat may also inhibit the absorption of cyclosporin and fat soluble vitamins.
Sibutramine	10 mg once daily, increased to 15 mg once daily if weight loss is less than 2 kg after four weeks.	Sibutramine acts on the serotonergic system therefore serotonergic medicines such as MAOIs and SSRIs should be avoided.
Phentermine	15 mg to 30 mg daily (usually 15 mg).	Phentermine can cause hypertension therefore it is best to avoid use of other medicines that increase blood pressure concomitantly.

There are few reports of serious adverse effects with phentermine. Common adverse effects include headache, insomnia, irritability, nervousness and palpitations.[6] Phentermine is frequently used as a weight loss medicine in the USA[16] and researchers are studying combinations of phentermine with taranabant,[17] topiramate[18] and bupropion for enhanced weight loss.

As there is limited data on the long-term effectiveness of phentermine, it is difficult to compare effectiveness (i.e. NNT) with orlistat or sibutramine.

Phentermine is available on prescription only and is not subsidised. The approximate cost to the patient for one months supply is $65 to $84 (depending on dose).

Fluoxetine

Fluoxetine is sometimes considered for use as a weight loss medicine, however there is mixed evidence of its effectiveness for this indication. Some studies have shown weight loss with fluoxetine,[19] while some show no effect.[20]

Fluoxetine is the anti-depressant of choice for people with obesity as it is not associated with weight gain, unlike many other antidepressants, including those in the SSRI class.

Metformin

Metformin has been shown to result in minor weight loss (1 to 2 kg) compared with placebo.[5, 7] This degree of weight loss is too low for metformin to be considered a weight loss medicine, however it may be a useful choice for overweight people at high risk of diabetes.[7]

Metformin is an insulin sensitiser that can be used in people who have central obesity, and particularly those with "obesity-related metabolic syndrome" or who are "pre-diabetic". Although nausea can occur, most people can adjust dose and timing (with meals) for comfort.

Review use of a medicine after 12 weeks if there has been a failure to achieve 5% weight reduction

Treatment should be reviewed regularly to assess effectiveness, adverse effects and adherence. These reviews should also be used as an opportunity to reinforce lifestyle advice. Medicine therapy should only be continued beyond 12 weeks if the patient has lost at least 5% of their initial body weight since starting. However, people with metabolic syndrome and type 2 diabetes may lose weight more slowly so less strict weight loss goals may be appropriate in these groups.[3, 4]

Maintenance of weight loss is difficult

Long term maintenance of weight reduction is difficult as physiological mechanisms modify energy balance to re-establish original body weight.[10] Patients are likely to regain weight after weight loss medicines are stopped.[4] It is important that lifestyle changes to diet and exercise are continued to maintain weight loss.[3] Successful strategies include a low energy/high fruit and vegetable diet, frequent monitoring of body weight and food intake and high levels of physical activity.[10]

Limited evidence for long term use of weight loss medicines

There is no strong evidence that long term use of weight loss medicines (i.e. over several years) leads to further weight loss beyond that lost in the first year, however people receiving follow-up achieve better results.[4] Studies have shown that when patients use weight loss medicines to maintain initial weight loss they still gain weight but regain less weight than those on placebo.[3]

Metabolic Syndrome

Although there has been a recent move away from using the term "metabolic syndrome" in guidelines, the concept is still supported and the definition has been recently up-dated.[21] Most people with metabolic syndrome have central obesity.

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