ARTICLE

Medicines for long-term obesity management

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Keywords
anti-obesity drugs, bupropion/naltrexone, hunger, liraglutide, orlistat, phentermine, semaglutide, topiramate, weight loss

Aust Prescr 2022;45:38–40
https://doi.org/10.18773/austprescr.2022.009

SUMMARY

Obesity is always genetic or epigenetic in origin in an obesogenic environment. Dietary therapy is required for weight loss.

Drugs to suppress hunger and increase satiety may assist while losing weight and are essential for most patients in the weight maintenance period. A combination of drugs may be needed.

A personalised approach must be used when selecting the appropriate weight loss drug for the patient. This considers possible contraindications, the method of administration and adverse effects, and includes discussing the cost of the treatment. Several drugs do not have an approved indication in Australia for weight loss.

Introduction

People with a body mass index above 30 kg/m^2 have obesity. There is strong evidence that obesity has a predominantly genetic[1] or epigenetic[2] basis. All other proposed causes of obesity, such as our modern lifestyle, gut bacteria and sleep deprivation, can modify weight but, on their own, cannot cause obesity. If a genetically thin person is put in an obesogenic environment, they will produce leptin which suppresses hunger. Although they will gain weight, they may not develop obesity.

Forced overfeeding studies from America have shown that, despite a group of individuals being overfed by the same amount, there is a range of weight gain. Those not gaining weight spontaneously increased their daily energy expenditure by around 2000 kilojoules.[3,4]

The genetic basis of obesity explains why the body defends weight so vigorously. Following even modest weight loss, there are long-lasting hormonal changes that lead to increased hunger and a reduction in energy expenditure.[5] This is why it may be helpful to consider using drugs to suppress hunger to assist with weight loss, depending on the diet being used to manage obesity. More importantly, these drugs are almost essential to help with maintaining the weight loss.

Drugs used in long-term management

There are several drugs for weight loss available in Australia (see Table),[6] however not all of them have an approved indication for obesity.

Phentermine

Phentermine is a sympathomimetic amine that acts on the brain to inhibit hunger.

Orlistat

Orlistat is an intestinal lipase inhibitor that slows fat digestion. It does not inhibit hunger, so it does not have a role in maintaining weight loss.

Liraglutide

Liraglutide is a glucagon-like peptide-1 (GLP-1) agonist with a hunger-suppressing action. It requires a daily injection with a starting dose of 0.6 mg. Liraglutide can cause nausea which settles after continued use. The dose can be slowly increased up to 3 mg daily, if required.

Semaglutide

Semaglutide 1 mg is approved in Australia for the treatment of type 2 diabetes. It is given as a weekly subcutaneous injection. Although GLP-1 agonists lower glucose in patients with diabetes, they do not cause hypoglycaemia in individuals who do not have diabetes. This is because GLP-1 requires elevated glucose concentrations to stimulate insulin secretion.

Low doses work very well in a subset of the population, but higher doses are needed by some. For these patients a 2.4 mg dose of semaglutide has been approved by the US Food and Drugs Administration (FDA) and is under consideration by the European authorities for the treatment of obesity. Compared to switching to placebo after 20 weeks, continued treatment with semaglutide can sustain weight loss.[7]

Bupropion with naltrexone

The combination of bupropion and naltrexone works by increasing activity in the melanocortin system of the hypothalamus. The starting dose is one tablet (bupropion 90 mg/naltrexone 8 mg) daily, gradually increasing to two tablets twice daily.

This article is peer-reviewed

Table **Drugs used in the maintenance of weight loss**

Drug	Doses available	Mode of action	Adverse effects	Contraindications	Efficacy (placebo subtracted losses)	Cost*
Phentermine	15, 30, 40 mg once daily	Sympathomimetic amine	Dry mouth Difficulty with sleeping Increased heart rate and blood pressure	Coronary artery disease Cardiac arrhythmias Use of antidepressant drug	6.4% weight loss	$145/month at highest dose
Orlistat	120 mg three times a day with meals	Intestinal lipase inhibitor	Steatorrhea	Pregnancy or breast feeding	4.1% weight loss	$92/month over-the-counter
Liraglutide 3 mg	0.6–3 mg once daily injection	Slows gastric emptying Suppresses hunger	Nausea Diarrhoea Constipation	History of pancreatitis	7.0% weight loss	$387/month at highest dose
Semaglutide	0.25–1 mg weekly injection	Slows gastric emptying Suppresses hunger	Nausea Diarrhoea Constipation	History of pancreatitis	8.6% weight loss	$132/month for 1 mg for patients without diabetes
Bupropion 90 mg/ naltrexone 8 mg	1–4 tablets daily	Increases melanocortin system activity	Nausea Constipation	Use of opioid analgesia Use of phentermine	6.3% weight loss	$242/month at highest dose
Topiramate	25–100 mg daily	Unknown	Paraesthesia Confusion Fetal abnormalities (cleft lip)	Glaucoma History of renal stones Pregnancy	7% weight loss	$22/month

* Costs in 2021

Topiramate

Topiramate is an antiepileptic drug. It has not been approved by the Therapeutic Goods Administration for the treatment of obesity in Australia because no one has applied to register it for treating obesity. However, topiramate in combination with phentermine was approved for the treatment of obesity by the FDA in 2012. Topiramate has frequent adverse effects that occur at higher doses. These include glaucoma, renal stones, paraesthesia and confusion. In addition, it has teratogenic effects on the developing embryo (cleft lip). The starting dose should be low (12.5–25 mg daily) for obesity management and the maximum dose should be 100 mg daily in two divided doses of 50 mg.

Considerations in drug selection

Drug therapy is part of the management of obesity. Clinical trials include diet and lifestyle interventions so patients still need to make lifestyle changes to benefit from drug treatment. When to start drug treatment depends on the diet being used for the management of obesity. For example, drugs may not be needed in ketogenic diets because ketones suppress hunger. The selection of the first drug to try is informed by the presence of any contraindications. A history of epilepsy excludes bupropion/naltrexone, pancreatitis excludes liraglutide and semaglutide, cardiac arrhythmia excludes phentermine, and glaucoma, renal stone disease and planning a pregnancy would exclude topiramate. The second consideration is cost and there is also a need to consider which drug would be the safest to use long term.

Efficacy and safety

A dose that works well with no adverse effects for one individual could cause very severe and intolerable adverse effects in another. All prescribers should warn their patients about this, then, by mutual agreement,

start one drug and be prepared to change to another if the first drug is not tolerated or is ineffective. Patients should be routinely monitored for adverse effects and the response to treatment.

Combination regimens

The body uses eight hormones to suppress hunger after a meal – cholecystokinin (CCK), peptide YY (PYY), glucagon-like peptide 1 (GLP-1), oxyntomodulin, uroguanilin, pancreatic polypeptide, amylin and insulin. It therefore makes sense that several drugs may be needed in combination to control hunger. If each medicine is used at a low dose, some of the adverse effects may be avoided. However, there is currently no evidence to support this approach.

Phentermine has been combined with topiramate and is available as a single capsule in the USA. In Australia, the two drugs can be prescribed separately.[8] Liraglutide or semaglutide could be combined with phentermine and topiramate or the bupropion/naltrexone combination. Phentermine should not be combined with bupropion/naltrexone. This is because bupropion has antidepressant effects and may increase cerebral serotonin. If that serotonin enters the blood stream, it normally would cause no harm, due to the avid uptake of serotonin by red blood cells. However, phentermine inhibits red cell uptake of serotonin so combining it with bupropion may increase circulating serotonin, which has been shown to cause heart valve fibrosis.

Treatment cost

Obesity rates are high in areas of low socioeconomic status. It is therefore important to consider the cost of the treatment when selecting a drug, a combination of drugs and the doses to be used. There is no subsidy for drugs that are approved for weight loss in Australia.

Duration of therapy

The hormone changes leading to increased hunger are very long lasting (at least six years, so probably life-long).[5] This should be taken into account when considering which drug should be chosen, in addition to dietary therapy, for the maintenance phase of weight loss.

Conclusion

Weight loss drugs are one part of the ongoing management of obesity. They are useful during the weight loss phase, but are essential in the maintenance phase. Patients need to be informed about the cost of these drugs, in addition to discussing efficacy and safety. <

Conflicts of interest: Joseph Proietto has been on the medical advisory boards for liraglutide, semaglutide 2.4 mg and bupropion/naltrexone. He has been involved in educational sessions for obesity management for both Novo Nordisk (liraglutide, semaglutide) and iNova (phentermine and bupropion/ naltrexone) for which he has received honoraria.

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