Pharmacotherapy for the management of overweight and obesity

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Background
Lifestyle intervention is the mainstay of obesity management; however, behavioural modification alone produces only modest results and attempts to create a negative energy balance are offset by a biological response to maintain weight. Pharmacotherapy is indicated as an adjunct for those living with obesity (body mass index [BMI] ≥30 kg/m^2) or those who are overweight (BMI ≥27 kg/m^2) with a least one weight-related complication.

Objective
This article provides an update on pharmacotherapy for the management of overweight and obesity.

Discussion
Pharmacotherapy is a useful adjunct for the treatment of obesity and obesity-related comorbidities. When considering pharmacotherapy, thought must be given to efficacy, contraindications, potential side effects, cost and duration of treatment.

OBESITY IS A CHRONIC disease affecting nearly one-third of Australian adults.[1] It is the result of a complex interplay of genetic, environmental and socioeconomic factors and is associated with a number of serious comorbidities including cardiovascular disease, cancer, type 2 diabetes and metabolic-associated fatty liver disease. Obesity contributes to reduced quality of life and premature mortality.[2]

Lifestyle intervention is the mainstay of obesity management; however, behavioural modification alone produces only modest results and attempts to create a negative energy balance are offset by a biological response to maintain weight.[3,4] Pharmacotherapy is indicated as an adjunct for those living with obesity (body mass index [BMI] ≥30 kg/m^2) or those who are overweight (BMI ≥27 kg/m^2) with a least one weight-related complication, including type 2 diabetes, dyslipidaemia, hypertension, metabolic-associated fatty liver disease, obstructive sleep apnoea and osteoarthritis. It can be used as an adjunct to lifestyle modification including energy restriction and increased physical activity. Weight loss of 5–15% has been shown to improve and/or prevent progression of obesity-related comorbidities, with greater weight loss resulting in more substantial improvements in complications and quality of life.[5,6] The risks and benefits of pharmacotherapy for the management of overweight and obesity, including the additional benefits on cardiometabolic disease and its risk factors, should be considered prior to initiation of therapy.

Unfortunately, pharmacotherapy for chronic weight management is not subsidised under the Pharmaceutical Benefits Scheme (PBS), and financial implications limit uptake of obesity-modifying medication for many Australians. Table 1 outlines the current pharmacotherapy available for the management of overweight and obesity in Australia and the estimated cost per month.

This article provides an update on pharmacotherapy for the management of overweight and obesity, highlighting the clinical efficacy, mechanism of action and considerations for use of each drug.

Pharmacotherapy

Therapeutic Goods Administration-approved pharmacotherapy

Incretin-based therapies

Several glucagon-like peptide 1 receptor agonists (GLP1-RAs) and a single GLP-1/glucose-dependent insulinotropic polypeptide (GIP) co-agonist are available in Australia and have been approved for the treatment of obesity. GLP-1 is a peptide

Table 1. Pharmacotherapy for the management of overweight and obesity

Drug	Mechanism of action	Expected weight loss	Starting dose	Available doses	Side effects	Contraindications	Monthly cost (2024)
Semaglutide[A,C] Wegovy®	GLP-1 analogue	10–15%	0.25 mg weekly	Flextouch pen 0.25 mg 0.75 mg 1.0 mg 1.7 mg 2.4 mg	Nausea, diarrhoea, abdominal pain, dyspepsia, abdominal distension, flatulence, gastroesophageal reflux, pancreatitis	Personal or family history of medullary thyroid cancer, MEN2, pregnancy	0.25–1 mg = $260[B] 1.7 mg = $380[B] 2.4 mg = $460[B]
Tirzepatide[A]	GIP/GLP-1 dual agonist	15–20%	2.5 mg weekly	Kwikpen 2.5 mg 5 mg 7.5 mg 10 mg 15 mg			2.5 mg = $285[B] 5 mg = $395[B] 5.5–10 mg = $545[B] 12.5–15 mg = $695[B]
Phentermine[A]/ Topiramate	NE agonist/ GABA agonist, glutamate agonist	4–6%	Phentermine 15 mg Topiramate 12.5 mg	15 mg, 30 mg, 40 mg 12.5 mg, 50 mg, 100 mg	• Phentermine: dry mouth, constipation, insomnia, closed angle glaucoma, agitation, depression, suicidal ideation • Topiramate: parasthesia, glaucoma, confusion, memory loss, renal stones, nausea, vomiting, pancreatitis	• Phentermine: severe hypertension, pulmonary arterial hypertension, existing valvular heart disease or heart murmur, arrythmia, advanced atherosclerosis, hyperthyroidism, glaucoma, psychiatric illness, MOI or SSRI use (or within 14 days of administration), pregnancy, breastfeeding, drug or alcohol dependence • Topiramate: glaucoma, renal stones, pregnancy	Phentermine $90–$170 Topiramate $15–$31
• Naltrexone/ bupropion[A]	• Opioid receptor agonist DA and NE reuptake inhibitor	4–5%	8 mg/90 mg	8 mg/ 90 mg	• Nausea, constipation, headache, vomiting, dizziness • Risk seizures, risk of opioid overdose, depression, suicidal ideation, hepatotoxicity, angle closure glaucoma	Uncontrolled hypertension, seizure disorder, opioid use disorder, anorexia or bulimia nervosa, abrupt discontinuation of alcohol, benzodiazapines, barbituates or antiepileptic drugs, during or within 14 days of taking an MOI, pregnancy	$249
Orlistat[A]	Gastric and pancreatic lipase inhibitor	2.9–8.5%	120 mg tds	120 mg	Steatorrhoea, flatulence, abdominal pain, fat-soluble vitamin deficiencies A, D, E, K	Malabsorption, pregnancy	$136

[A]Therapeutic Goods Administration (TGA) approved.

[B]Cost per pen device. Each pen contains 4 doses.

[C]Semaglutide is available in Australia in two forms: Ozempic® (1 mg) is TGA approved for the management of type 2 diabetes; and Wegovy® (2.4 mg) is TGA approved for the management of obesity.

DA, dopamine; GABA, gamma-aminobutyric acid; GIP, gastric inhibitory polypeptide; GLP-1, glucagon-like peptide 1; MEN2, multiple endocrine neoplasia 2; MOI, monoamine oxidase inhibitor; NE, norepinerphrine; SSRI, selective serotonin reuptake inhibitor.

hormone secreted by the enteroendocrine cells of the distal small intestine. GLP1-RAs exert their effects by acting on GLP-1 receptors in the pancreas, stomach, brain, kidney, heart and adipose tissue. Activation of GLP-1 receptors in the hypothalamus and mesolimbic pathways results in appetite suppression, reduction in food cravings and a reduction in total caloric intake. GLP1-RAs enhance glucose-dependent insulin secretion, reduce glucagon secretion and delay gastric emptying making them effective drugs for the treatment of type 2 diabetes and obesity. GIP is a peptide hormone secreted by the enteroendocrine cells of the proximal small intestine. GIP receptors are found in the pancreas, adipose tissue, brain, bone, heart, lung, blood vessels and gastrointestinal tract. Of the two incretins, GIP has been shown to have a greater effect on insulin release following oral glucose ingestion in humans. Unlike GLP-1, pharmacological doses of GIP do not lower appetite and GIP does not slow gastric emptying. GIP increases adipose tissue insulin sensitivity and blood flow, reducing free fatty acid release. The dual GLP-1/GIP co-agonist, tirzepatide, has demonstrated superior efficacy in comparison to GLP1-RAs in reducing plasma glucose and bodyweight. There has been increasing interest in the therapeutic effects of incretin-based therapies in the management of overweight and obesity. Studies with semaglutide or tirzepatide have demonstrated benefit in heart failure with preserved ejection fraction,[7,8] metabolic-associated fatty liver disease,[9,10] knee osteoarthritis,[11] obstructive sleep apnoea[12] and in secondary prevention of cardiovascular disease.[13] Ongoing clinical trials are investigating the potential benefits of incretin-based therapies for neurodegenerative disorders such as Alzheimer's disease through mitigation of neuroinflammation and a reduction in amyloid-beta plaque deposition;[14] Parkinson's disease; atrial fibrillation; and alcohol use disorder and opioid addiction.[15]

Semaglutide

Semaglutide (Wegovy®; Novo Nordisk, Bagsv ærd, Gladsaxe, Denmark) is a GLP1-RA administered once weekly by subcutaneous injection. It has demonstrated efficacy for weight loss in patients with and without type 2 diabetes mellitus (T2DM) and has shown improvement in obesity-related comorbidities including a reduction in death from cardiovascular causes, non-fatal myocardial infarction and non-fatal stroke in patients with pre-existing cardiovascular disease.[13] The initial dose of semaglutide is 0.25 mg once weekly with dose escalation every four weeks to a maximum dose of 2.4 mg weekly, for those with obesity. If the dose is not tolerated (ie nausea, vomiting, diarrhoea, constipation), then a more gradual dose escalation is suggested.

Semaglutide is currently available in two forms: Ozempic® (Novo Nordisk, Bagsværd, Gladsaxe, Denmark; approved and PBS subsidised for the treatment of T2DM, maximum dose 1 mg weekly) and Wegovy® (approved as an adjunct to lifestyle modification for chronic weight management, maximum dose 2.4 mg weekly). Wegovy® has recently been Therapeutic Goods Administration (TGA) approved as an adjunct to standard of care to reduce the risk of adverse major cardiovascular events in adults with established cardiovascular disease and a BMI of ≥27 kg/m^2. Ozempic® is not TGA approved for weight management.

Wegovy® is not currently subsidised under the PBS and is only available via private prescription. An escalation in dose also results in an increase in cost to the consumer (Table 1); however, if weight loss is acceptable, there is no need to escalate the dose and many patients achieve successful weight loss outcomes on low–mid doses.

The Semaglutide Treatment Effect in People with Obesity (STEP1) trial assigned 1961 patients with obesity (without T2DM) to 68 weeks of treatment with 2.4 mg semaglutide or placebo plus lifestyle intervention. Those in the semaglutide group lost a mean 14.9% compared with 2.4% in the placebo group, and 69.1% of patients in the semaglutide group achieved >10% weight loss with 50.5% of patients achieving >15% body weight loss.[16]

The majority of adverse events are gastrointestinal, but are generally mild to moderate and transient (Table 1).[16] More serious gastrointestinal adverse events have been reported and include pancreatitis and gastroparesis; however, a meta-analysis of cardiovascular outcomes trials in subjects with T2DM did not detect a signal for acute pancreatitis.[17,18] More recently, there have been reports of a potential increased risk of non-arteritic anterior ischaemic optic neuropathy in patients using semaglutide; however, future studies are required to assess causality.[19]

Tirzepatide

Tirzepatide is a dual GIP and GLP-1 receptor co-agonist. Tirzepatide is administered once weekly at a starting dose of 2.5 mg, with the dose increased to 5 mg weekly after four weeks. If needed, dose increases can be made in 2.5-mg increments with a minimum of four weeks on each dose. A decision to increase the dose should be based on efficacy and tolerability, with a maximum dose of 15 mg once weekly. No dose adjustment is needed in patients with renal or hepatic impairment. Similar to GLP1-RAs, the most common side effects are gastrointestinal and are usually transient.

Randomised controlled trials (RCTs) have shown significant weight loss in subjects with and without T2DM. An RCT of 2500 subjects with overweight or obesity (without T2DM) showed a mean percentage bodyweight loss of 15, 19.5 and 20.9% in patients taking 5 mg, 10 mg and 15 mg of tirzepatide, respectively.[20] In addition, tirzepatide has shown a significant improvement in obesity-related comorbidities including obstructive sleep apnoea (OSA), metabolic-associated fatty liver disease and heart failure with preserved ejection fraction (HFpEF).[8,10,12]

Liraglutide

Liraglutide is a once-daily GLP1-RA. It is administered via subcutaneous injection at a starting dose of 0.6 mg weekly with slow up-titration to a maximum dose of 3.0 mg weekly. It has a similar side effect profile to other GLP1-RAs. A 56-week, placebo-controlled trial of liraglutide 3 mg plus lifestyle intervention resulted in a mean weight loss of 8% compared with 2.6% in the placebo group.[21]

Phentermine

Phentermine can be used as monotherapy or prescribed with off-label topiramate for a synergistic effect. Phentermine is a sympathomimetic agent that is TGA approved for the treatment of obesity. It exerts its weight loss effects through

potent appetite suppression. It is given as a single, daily oral dose, starting with 15 mg and can gradually be up-titrated if required, though sympathomimetic side effects limit tolerability and long-term use. Phentermine is contraindicated in patients with cardiovascular disease, cerebrovascular disease and uncontrolled hypertension (Table 1). A thorough cardiovascular history and examination should be performed prior to prescribing, with close monitoring of heart rate, blood pressure and mood at baseline and three months. Phentermine is an effective drug for weight loss in the short term (ie 12 weeks); however, it can be used in the longer term in carefully selected patients.

Phentermine is relatively affordable and modestly effective. A randomised double-blind placebo controlled trial of 12 weeks of treatment with phentermine 30 mg or placebo showed significant reductions in bodyweight (−8.1±3.9 vs −1.7±2.9 kg) compared with placebo. Weight reductions of 5% or greater from baseline (95.8 vs 20.8%, $P< 0.001$) and 10% or more (62.5 vs 4.7%, $P<0.001$) were achieved in the phentermine group versus placebo group, respectively, without clinically significant adverse events.[22] Similarly, a clinical trial of phentermine 30 mg resulted in a 12.2-kg weight loss over 36 weeks compared with 4.8 kg in the placebo group.[23]

Naltrexone/bupropion

Naltrexone/bupropion is an oral, TGA-approved weight loss medication. The combination of naltrexone/bupropion works synergistically in the hypothalamus and mesolimbic dopamine circuit to induce satiety, reduce cravings and reduce caloric intake.[24] Each tablet contains 8 mg naltrexone and 90 mg bupropion. Gradual dose escalation improves tolerability. Patients should be advised to commence one tablet in the morning for one week. Following this, a second tablet should be taken in the evening. If weight loss response is insufficient, the dose can be gradually escalated to a maximum dose of two tablets twice daily. Dose adjustments are required for patients with renal and hepatic impairment. Concomitant use with a CYP2B6 inhibitor should be avoided; however, if this is not possible, the maximum dose of naltrexone/bupropion should be reduced to one tablet twice daily.[25]

Four phase 3 RCTs have examined the effect of total bodyweight loss in patients with obesity using naltrexone/bupropion.[26–28] Naltrexone/bupropion resulted in approximately 5–8% weight loss, with a mean change in bodyweight of −6% in the treatment group versus −1.3% in the placebo group by intention-to-treat analysis.[28] Only 50% of participants completed the 56 weeks of treatment.

Orlistat

Orlistat is a potent inhibitor of gastric and pancreatic lipase resulting in reduced fat absorption and loss of weight. The recommended dose of orlistat is 120 mg three times daily (tds) with a fat-containing meal. Side effects are related to fat malabsorption and include oily stool leakage, steatorrhoea and fat-soluble vitamin deficiencies. Gastrointestinal side effects are the main reason for discontinuation of therapy. A double-blind, randomised, placebo-controlled trial of adults with obesity assigned to 120 mg tds of orlistat along with a low-energy diet (with 30% of energy from fat) showed an average 8.5% initial bodyweight loss compared to 4.5% with placebo.[29] Similarly, a Cochrane meta-analysis of 15 studies showed that orlistat reduced weight by 2.9 kg or 2.9% more than placebo.[30]

Off-label pharmacotherapy

Topiramate

Topiramate is an anticonvulsant that is used off label for the treatment of obesity. Patients prescribed topiramate monotherapy lose an estimated 3.4–5.0 kg.[31,32] It is often used in combination with phentermine, but dose-dependent side effects limit use. Topiramate can be started at a dose of 12.5 mg once daily and up-titrated to 50 mg twice daily.

A fixed dose of phentermine/topiramate (extended release) was Food and Drug Administration (FDA) approved in 2012 in the United States. It is not available as a fixed-dose combination in Australia. When combined, phentermine/topiramate (7.5/46 mg or 15/92 mg) results in an estimated 8–10 kg bodyweight loss in 12 months; however, only 61% of participants completed treatment and we cannot assume the same efficacy when prescribed as combined, single agents.[33]

Other off-label pharmacotherapy

Dulaglutide, sodium–glucose cotransporter 2 (SGLT2) inhibitors and metformin are not recommended for chronic weight management but are useful in the management of T2DM and can result in very modest weight reduction.

Choice of therapy and special considerations

Lifestyle interventions and multidisciplinary support are crucial for successful weight loss. For patients with a BMI of 30–39.9 kg/m^2, without obesity-related complications, supervised lifestyle modification and initiation of pharmacotherapy can be undertaken in the primary care setting. An initial assessment should be undertaken, with a focus on medical (diabetes, cardiometabolic, metabolic associated fatty liver disease [MAFLD], OSA, polycystic ovarian syndrome [PCOS], osteoarthritis) and psychological complications, including assessment for the presence of disordered eating. Generally, follow-up should occur at one-monthly intervals to assess medication tolerance during dose escalation and one-to-three-monthly intervals thereafter to encourage adherence to therapy and assess progress. Specialist care should be considered for those with obesity-related comorbidities or for those with a BMI of >40 kg/m^2. If patients fail to lose 5% of total bodyweight after 12 weeks on the maximum dose of pharmacotherapy, consideration should be given to cessation of therapy and the trial of an alternative agent.

For patients with T2DM, cardiovascular disease, knee osteoarthritis, OSA or MAFLD, incretin-based therapies (GLP1-RA or dual GLP1-RA/GIP) should be considered first line because of the significant improvements in obesity-related complications (eg OSA, heart failure with preserved ejection fraction, MAFLD, T2DM) with these drugs. For patients without cardiovascular disease or hypertension, phentermine/topiramate or naltrexone/bupropion are reasonable options if there are no other contraindications. Orlistat can be considered in patients with cardiovascular disease or hypertension where incretin-based therapies are not tolerated or unaffordable.

Blood pressure should be monitored routinely after initiation of pharmacotherapy and antihypertensives should be down-titrated as required. Similarly, close monitoring of blood glucose levels is required in those with diabetes and consideration should be given to reduction in glucose-lowering medications, particularly insulin and sulfonylureas.

As obesity is a chronic condition, most individuals require lifelong therapy. Treatment discontinuation is associated with weight regain and recurrence of weight-related comorbidities for the majority of individuals who cease obesity-modifying medication, with a loss of the metabolic benefits achieved on pharmacotherapy including reductions in blood pressure and improvements in glycaemia and blood lipids.[34] Maintenance of weight loss with lifestyle measures rather than pharmacotherapy is possible but requires intensive lifestyle modification and support, with weight regain occurring once intensive behavioural support is withdrawn.[35]

All pharmacotherapy options for the treatment of obesity are contraindicated during pregnancy and lactation, and women should be advised to cease anti-obesity medications at least two months prior to trying to conceive.[36]

Conclusion

Pharmacotherapy is a useful adjunct for the management of overweight, obesity and obesity-related comorbidities. Consideration should be given to the use of pharmacotherapy in those with a BMI of ≥30 kg/m^2 or ≥27 kg/m^2 with obesity-related comorbidities. When considering pharmacotherapy, thought must be given to efficacy, contraindications, potential side effects, cost and duration of treatment.

Key points

- Obesity is a chronic disease that is associated with a number of serious comorbidities including cardiovascular disease, cancer, T2DM and MAFLD.
- Lifestyle modification alone achieves only modest weight loss and weight regain is common.
- Pharmacotherapy is indicated as adjunctive therapy for those living with obesity (BMI ≥30 kg/m^2) or those who have overweight (BMI ≥27 kg/m^2) with a least one weight-related complication.
- Pharmacotherapy for the treatment of obesity is not currently PBS reimbursed, resulting in equity issues in accessing obesity-modifying medication.
- Cessation of pharmacotherapy can lead to weight regain. Pharmacotherapy should always be combined with lifestyle modification.

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