Managing obesity

Looking beyond lifestyle interventions

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Most people in Australia are overweight or have obesity. Obesity and its complications result in excess morbidity and mortality and a reduced quality of life, as well as a substantial financial burden to people and healthcare systems. Effective treatment options for obesity are available, and promising new therapies are under investigation in clinical trials.

Key points

- **Almost one in three Australian adults has obesity.**
- **Effective treatments for obesity are available, which reduce morbidity and improve peoples' health and quality of life.**
- **When the treatment goals are not met or are unlikely to be met by lifestyle interventions alone, medications and surgical management should be considered.**
- **GPs play a key role in supporting patients to manage obesity.**

Obesity is a medical condition that heightens the risk of other health issues, such as diabetes, cardiovascular disease and hypertension. This article provides an overview of current and emerging pharmacological and surgical management approaches for obesity.

What is obesity?

Obesity refers to abnormal or excessive fat accumulation that presents a risk to a person's health.[1] A body mass index (BMI) greater than 30 kg/m^2 is also used to define obesity, although the BMI alone does not indicate a person's health status. Obesity is a complex chronic condition that develops in genetically predisposed people in response to several (predominantly environmental) factors.[2]

Why is it important to treat obesity?

Obesity affects almost one-third (31%) of adults in Australia and is the second largest contributor to the country's burden of disease, primarily because of its numerous complications.[3,4] Much of the adverse impact of obesity on health and quality of life can be reduced with weight loss; hence, effective treatment is critical (Table 1).[5] Loss of just 5% of the original body weight reduces the risk of progression to type 2 diabetes by more than 50% in people with impaired glucose tolerance, as well as improving blood pressure and triglyceride levels.[6] Greater weight loss (in the order of 10 to 25%) has progressive benefits, including improvements in the control (and potentially remission) of type 2 diabetes, fatty liver disease, obstructive sleep apnoea, stress urinary incontinence and symptoms of osteoarthritis, and improvements in health-related quality of life.[7] Until recent years, most

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Table 1. Expected benefits of weight loss on selected chronic diseases[5]

Diagnosis	Weight loss (%)	Expected benefit of weight loss
Type 2 diabetes	5 to 15	Prevention of diabetes and reductions in glycated haemoglobin levels and the need for diabetes medications; diabetes remission if duration is short (weight loss >10%)
Dyslipidaemia	5 to 15	Lower triglyceride levels
Hypertension	5 to 15	Lower blood pressure and reduction in medication doses
Nonalcoholic fatty liver disease	10 to 40	Reduction in hepatic steatosis and steatohepatitis
Polycystic ovary syndrome	5 to 15	Ovulation, reduction in hirsutism, decreased androgen levels and increased insulin sensitivity
Obstructive sleep apnoea	7 to 11	Decreased apnoea–hypopnoea index
Asthma	7 to 8	Improved forced expiratory volume in one second
Gastro-oesophageal reflux disease	>10	Reduced symptoms

interventions for obesity apart from bariatric surgery were expected to achieve sustained weight loss of less than 5%, but an increasing number of effective nonsurgical approaches is becoming available.[8]

What role do GPs play?

Obesity requires lifelong monitoring and management. GPs are essential in establishing a diagnosis of obesity and in managing obesity at each stage of the treatment pathway. The 5 A's framework is a guide to obesity management in the primary healthcare setting (Box).[5,9] Specialised obesity services are scarce and often need to limit the care provided, such as for people with genetic obesity syndromes or severe complications; these services may also have long (more than one year) waiting times.[10] Therefore, obesity often needs to be managed largely or entirely within the primary healthcare setting. With the benefit of an established therapeutic relationship, primary healthcare practitioners are ideally placed to advise and support behaviour change; discuss, initiate and adjust medications when needed; refer to additional clinicians and services (e.g. dietitian, exercise physiologist, psychologist, specialist physician or surgeon) where required; monitor progress; and address challenges that arise during obesity treatment. The Australian Obesity Management Algorithm also provides guidance on the assessment and management of obesity in the primary healthcare setting.[11]

What lifestyle interventions are effective?

The main purpose of lifestyle interventions in obesity management is to reduce energy intake, optimise nutritional quality and increase physical activity. This can be accomplished via a variety of approaches, with no single dietary pattern showing superiority. An individualised regimen supported by a multidisciplinary team with frequent contact (14 or more sessions across six to 12 months) has been shown in clinical trials to be the most effective approach;[9] however, this degree of allied healthcare support is not subsidised by Medicare.

Most people who lose weight with lifestyle interventions alone will regain weight in the longer term. The misconception that obesity is simply caused by poor lifestyle habits and inadequate motivation for behaviour change is common and leads to stigma. However, weight loss leads to an enduring biological response that results in an increased appetite and a reduction in total energy expenditure (more than expected for the loss of body mass). Interactions between biological, psychosocial and 'obesogenic' environmental factors make the maintenance of weight loss challenging for most people.

Framework for obesity management in the primary healthcare setting[5,9]

Ask and Assess
- Routinely assess and monitor body mass index and waist circumference
- Discuss the health impacts of obesity
- Screen for and manage comorbidities and complications, including changes in blood pressure, lipid levels, fasting glucose and glycated haemoglobin levels, liver function and symptoms of sleep apnoea and depression
- Use nonjudgemental language, avoiding weight-related stigma

Advise
- Promote the benefits of a healthy lifestyle, using a motivational interviewing approach
- Explain the benefits of weight management in terms of health outcomes
- Set a realistic target and time frame for weight loss

Assist
- Using an individualised approach, create an obesity management program considering all options appropriate to the situation (including lifestyle interventions, pharmacotherapy and bariatric surgery)
- Consider a referral to a dietitian and exercise physiologist through a GP Chronic Disease Management plan

Arrange
- Organise a review for follow up
- Consider a referral to a specialist obesity management service for patients with complex needs

What pharmacotherapy is available?

Five medications are approved by the Therapeutic Goods Administration (TGA) for obesity management: liraglutide, semaglutide, phentermine, naltrexone-bupropion and orlistat (Table 2), although at the time

Table 2. Medications for obesity management[11]

Medication	TGA-approved indication	Formulation	Starting dose	Titration	Maximum dose	Contraindications	Adverse effects	Approximate cost per month*
Liraglutide	Chronic weight management	Subcutaneous injection	0.6 mg daily	Increase by 0.6 mg daily per week	3.0 mg daily	Pregnancy or lactation, personal or family history of medullary thyroid cancer or multiple endocrine neoplasia type 2	Nausea, vomiting, diarrhoea, constipation, cholecystitis	$387
Semaglutide	Chronic weight management	Subcutaneous injection	0.25 mg weekly	Increase every four weeks (0.5 mg, 1.0 mg, 1.7 mg, 2.4 mg)	2.4 mg weekly			Unknown (unavailable in Australia at the time of writing)
Phentermine	Short-term weight management	15, 30 and 40 mg capsules	15 mg daily	N/A	40 mg in the morning	Uncontrolled hypertension, cardiac disease, glaucoma, history of drug abuse, MAO inhibitor or SSRI use, pregnancy or lactation	Hypertension, tachycardia, insomnia, anxiety or depression, restlessness, dry mouth, diarrhoea	$108 to $145
Naltrexone/ bupropion	Chronic weight management	Tablets containing 8 mg naltrexone and 90 mg bupropion	8 mg/90 mg daily	Increase by one tablet weekly	16 mg/180 mg twice daily	Uncontrolled hypertension, seizure disorder or history of seizures, bipolar disorder, acute alcohol or benzodiazepine withdrawal, pregnancy or lactation, severe hepatic impairment, MAO inhibitor use	Nausea, constipation, dizziness, headache, insomnia, dry mouth	$240
Orlistat	Chronic weight management	120 mg tablets	120 mg three times a day with meals	N/A	120 mg three times a day	Fat-soluble vitamin deficiency, chronic malabsorption, cholestasis, pregnancy or lactation	Steatorrhoea, oily leakage, excessive flatus, fat-soluble vitamin deficiency	$93
Topiramate†	Epilepsy and migraine prophylaxis	25 mg and 50 mg tablets	12.5 mg in the morning	Increase by 25 mg every two to four weeks	50 mg twice daily	Glaucoma, renal stones, pregnancy or lactation	Paraesthesia, memory impairment, glaucoma, renal stones, taste disturbance	$11

Abbreviations: MAO = monoamine oxidase inhibitor; SSRI = selective serotonin reuptake inhibitor; TGA = Therapeutic Goods Administration.

* Cost per month at the recommended dose, estimated from pharmacy websites in February 2023.

† Not TGA-approved for obesity.

Adapted from the Australian Obesity Management Algorithm

of writing, semaglutide 2.4 mg weekly is not yet available in Australia.[11] Orlistat, liraglutide, naltrexone/bupropion and semaglutide are indicated for adults (18 years of age or older) with a BMI higher than 30 kg/m^2, or higher than 27 kg/m^2 with a weight-related complication. Phentermine is approved for adults and adolescents older than 12 years of age with a BMI of 25 kg/m^2 or higher. No medications are subsidised by the PBS for obesity management.

The choice of medication requires the consideration of a number of individualised factors, including the patient's preference, severity of obesity, presence of obesity-related and unrelated medical conditions and the medication's contraindications, adverse effect profile and costs. All the medications approved for obesity management are contraindicated during pregnancy and lactation.

Glucagon-like peptide-1 receptor agonists

Two glucagon-like peptide-1 (GLP-1) receptor agonists are currently TGA-approved for obesity management: liraglutide (dosage of 3.0 mg daily) and semaglutide (dosage of 2.4 mg weekly). Liraglutide (dosage of up to 1.8 mg daily) and semaglutide (dosage of up to 1.0 mg weekly) are also indicated for the treatment of type 2 diabetes, as is dulaglutide (dosage of 1.5 mg weekly). Semaglutide 1.0 mg weekly and dulaglutide are PBS-subsidised for management of diabetes in people with a glycated haemoglobin level greater than 53 mmol/mol (7.0%). In clinical trials for obesity management in people without diabetes, the mean total weight losses were 8% (*vs* 2.6% in the placebo group) in those taking liraglutide 3.0 mg daily for 56 weeks and up to 16% (*vs* 5.7% in the placebo group) in those taking semaglutide 2.4 mg weekly for 68 weeks.[12,13]

GLP-1 receptor agonists act via GLP-1 receptors. In the brain (particularly in the hypothalamus and hindbrain), they act to increase satiety and reduce hunger and food reward. In the pancreas and gastrointestinal tract, they slow gastric emptying, enhance insulin release in the presence of elevated glucose levels and reduce glucagon release.

Their beneficial effects on glycaemia make them particularly suitable for obesity management in people with (or at a high risk of) type 2 diabetes.[13] At doses used to treat type 2 diabetes, some GLP-1 receptor agonists (e.g. dulaglutide, liraglutide and semaglutide) reduce mortality and risks of cardiovascular and renal disease in patients with diabetes;[14] however, these benefits have not yet been shown at the higher doses used to treat obesity in people without diabetes, who have lower risks of cardiovascular and renal disease.

The adverse effects include nausea, vomiting, constipation, diarrhoea and an increased risk of cholelithiasis and cholecystitis. Nausea usually improves with continued therapy and can be minimised by starting the medication at a low dosage and gradually uptitrating.

Phentermine

Phentermine is a sympathomimetic agent that stimulates the release of noradrenaline, dopamine, and serotonin in several areas of the brain to reduce hunger and reward-related eating. It is indicated as a 'short-term adjunct' in a medically monitored obesity management program, with patients requiring medical review within three months. The weight loss within 12 weeks is typically five to 10%.[15] Common adverse effects include tachycardia, hypertension, insomnia and dry mouth. Phentermine is contraindicated in people with cardiovascular disease or uncontrolled hypertension and those taking monoamine oxidase inhibitors. Phentermine is also not recommended in combination with selective serotonin reuptake inhibitors.

Naltrexone-bupropion

This combination of an antidepressant (bupropion) and opioid antagonist (naltrexone) acts in the hypothalamus and mesolimbic reward system to reduce hunger and food cravings. In a 56-week randomised trial, naltrexone-bupropion resulted in a mean weight loss of 6.1% (compared with 1.3% in the placebo group).[16]

The adverse effects include nausea, headache, dizziness, insomnia and dry mouth. Naltrexone-bupropion is contraindicated in patients with a history of seizures or bipolar disorder and in those using opioid medications. Several potential drug interactions are relevant when prescribing naltrexone-bupropion, particularly those involving cytochrome P450 enzyme activity, including a consideration of dose reductions of medications metabolised by CYP2D6 (including selective serotonin reuptake inhibitors, because of CYP2D6 inhibition by bupropion) if prescribed concurrently.

Orlistat

Orlistat reduces gastrointestinal fat absorption by inhibiting pancreatic and gastric lipases. Unlike other obesity medications, orlistat is not systemically absorbed, having only local action in the gut lumen. Weight loss of about 5% is expected after one year of treatment.[17]

The safety and modest efficacy of orlistat have been shown in randomised trials of up to four years' duration,although the adherence to treatment is poor, largely because of its gastrointestinal adverse effects.[17] Common adverse effects include steatorrhoea, oily stools and flatulence. The absorption of fat-soluble vitamins may be reduced by orlistat; therefore, a multivitamin should be advised. Orlistat has a weight loss-independent effect on lowering LDL (by 28% compared with that by lifestyle interventions).[18]

Other agents

Topiramate

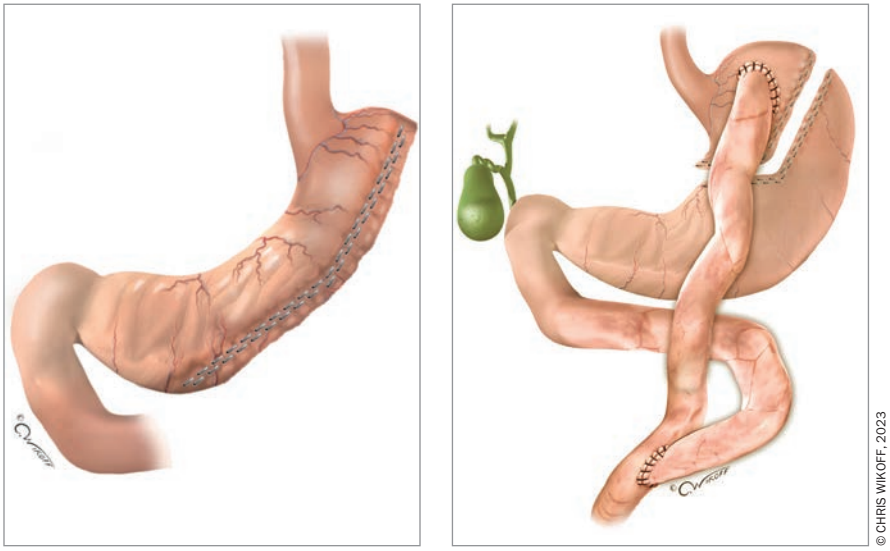
Topiramate is approved for the treatment of epilepsy and the prevention of migraine. It is commonly used off-label for obesity management, although the drug's mechanism of action for weight loss is unclear. In the United States (but not in Australia), a combination of extended-release topiramate and phentermine is approved for obesity management. Meta-analyses of data from randomised controlled trials of topiramate for obesity suggest weight loss of about 5% compared to that with placebo.[19,20] The adverse effects include gastrointestinal disturbances, difficulties concentrating, paraesthesia, depression, teratogenicity and (rarely) closed-angle glaucoma.

Table 3. Advantages and disadvantages of bariatric surgery[23-26]

Procedure	Advantages	Disadvantages
Sleeve gastrectomy	• A mean total weight loss of about 20% at five years • Simpler procedure • Anastomosis not required • Few long-term complications	• Higher risk of weight regain or insufficient weight loss • Worsening or de novo gastro-oesophageal reflux disease in about 30%
Roux-en-Y gastric bypass	• A mean total weight loss of about 25% at five years • Higher likelihood of sustained remission of type 2 diabetes • Can be used as a revisional procedure after sleeve gastrectomy	• Higher risk of early major complications (<5%) and long-term micronutrient deficiencies

Tirzepatide

Tirzepatide is a dual agonist that acts at GLP-1 and glucose-dependent insulinotropic polypeptide receptors. It is TGA-approved for the treatment of type 2 diabetes at dosages of 5, 10 and 15 mg once weekly but is not yet available in Australia at the time of writing. Tirzepatide is the first medication to show a mean weight loss of more than 20% in clinical trials for obesity management, and regulatory assessment for an obesity indication is expected to be sought in 2023. In a phase 3 clinical trial, participants taking tirzepatide 5, 10 and 15 mg achieved weight loss of 15%, 20% and 21%, respectively, after 72 weeks of treatment, compared with 3% with placebo.[21] The adverse effects are predominately gastrointestinal, with a profile similar to that of GLP-1 receptor agonists.



Figures 1a and b. Bariatric surgery. The most common approaches are sleeve gastrectomy (a, left) and Roux-en-Y gastric bypass (b, right).

When should pharmacotherapy be reviewed?

Patients should be monitored at least monthly for the first three months after initiating pharmacotherapy to assess safety and efficacy and review the need for dose titration.[5] Early weight loss is predictive of longer-term weight loss; hence, weight loss of less than 5% after three months at the recommended dose requires a change in the treatment strategy.[5] It is worth noting that if a medication is initiated to prevent or minimise weight regain (rather than to induce weight loss), weight stability (rather than continued weight gain) may still indicate a beneficial effect. Weight regain is likely after cessation of pharmacotherapy;[22] therefore, long-term treatment is likely to be required (as for most chronic diseases), although data on the long-term efficacy and safety of obesity medications are currently lacking.

What is the role of bariatric/metabolic surgery?

More than 40,000 individuals are estimated to undergo bariatric surgery each year in Australia.[23] The most common operations are sleeve gastrectomy and Roux-en-Y gastric bypass (RYGB) (Table 3) (Figure 1), both of which help achieve substantial, sustained weight loss.[23-26] Compared with sleeve gastrectomy, RYGB results in greater mean weight loss (at five years, around 25% after RYGB and 19% after sleeve gastrectomy in an observational cohort study [n = 65,000]) with a higher risk of major complications (at 30 days, 5.0% after RYGB and 2.6% after sleeve gastrectomy).[24] Substantial weight regain, defined as regain to within 5% of pre-operative weight, occurs in fewer than 5% of patients after RYGB and in around 10% of patients after sleeve gastrectomy.[27]

Australian guidelines recommend that bariatric surgery be considered in patients with the following BMIs and presentations:

- BMI 40 kg/m^2 or higher
- BMI 35.0 to 39.9 kg/m^2 and comorbidities that may improve with weight loss
- BMI 30.0 to 34.9 kg/m^2, suboptimal control of type 2 diabetes and increased risk of cardiovascular disease.[9]

International guidelines were updated in 2022 to recommend bariatric surgery for people with a BMI of 35 kg/m^2 or higher, regardless of the presence, absence or severity

of obesity-related conditions.[28] Surgery should not be viewed only as a last resort for those in whom other obesity treatments have 'failed'. For example, in patients with suboptimal glycaemic control on maximum medical management of type 2 diabetes, early referral to surgery should be considered. Access to bariatric surgery is limited and inequitable because of a lack of services, particularly in the public sector,with about 90% of bariatric surgeries occurring in the private healthcare system in Australia.[29,30]

A multidisciplinary team approach is imperative to assess the potential benefits and risks of bariatric surgery for each patient before surgery, as well as for preoperative preparation and postoperative follow up. After bariatric surgery, patients require lifelong nutritional supplementation, monitoring and ongoing support, although guidelines differ in terms of specific recommendations.[25,31]

What nonsurgical procedures are available?

Endoscopic insertion of a fluid- or air-filled intragastric balloon is a nonsurgical option for obesity management. This is a temporary procedure, with the balloon removed after around six months (depending on the specific product). This procedure aims to reduce food intake by reducing gastric capacity and delaying gastric emptying. Weight loss achieved in clinical trial settings is about 4% greater compared with that in lifestyle intervention groups after three to six months.[32] Longer-term data are scarce. The adverse events include nausea, abdominal pain, deflation and (rarely) gastric perforation.

Conclusion

The goals of obesity management are to improve a person's health and quality of life. Many patients will not achieve the goals of treatment using lifestyle interventions alone. Several obesity medications and bariatric surgeries are available. The latest generation of medications is associated with mean weight losses that are close to the magnitude seen with bariatric surgery. However, there are inequities in accessibility at every stage of obesity care. **ET**

References

A list of references is included in the online version of this article (www.endocrinologytoday.com.au).

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