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Focus on obesity

Managing obesity – looking beyond lifestyle interventions

A clinical approach to managing obesity in adults

New pharmacological treatments for obesity: incretin analogues, their mechanism of action, efficacy and safety

Concurrent management of type 2 diabetes and obesity

Targeting the weight within – obesity pharmacotherapy in cardiovascular disease

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SYDNEY OFFICE
Suite 503, Level 3
116 Military Road
Neutral Bay NSW 2089

POSTAL ADDRESS
PO Box 1473, Neutral Bay NSW 2089

TELEPHONE (02) 9908 8577
FACSIMILE (02) 9475 0645

EMAIL
Editorial enquiries
reception@medicinetoday.com.au
Production enquiries
mariamarmora@medicinetoday.com.au
Advertising sales enquiries
prueanderson@medicinetoday.com.au
General enquiries
reception@medicinetoday.com.au

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THE PEER REVIEWED JOURNAL OF CLINICAL PRACTICE

FOREWORD FROM THE COLLECTION EDITOR

Obesity is one of the most pressing and multifaceted challenges in contemporary healthcare. Affecting almost one in three Australian adults, it carries profound implications for quality of life, mortality and health system burden. This *Focus on obesity* collection presents a timely and practical overview of the current landscape of obesity management in general practice.

The collection begins with a broad clinical approach to managing obesity in adults, reinforcing the need to treat obesity using a chronic disease model of care and the requirement for long-term, individualised care.

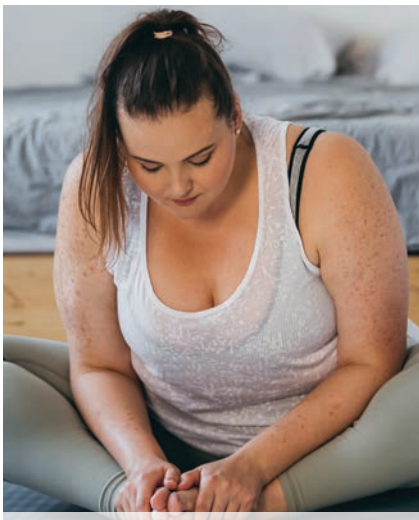
An update on pharmacological advances focusing on the incretin analogues details their impressive efficacy, mechanisms of action and real-world limitations. The management of obesity in the context of common comorbidities is explored in depth, with focused articles on type 2 diabetes and cardiovascular disease, both of which intersect with obesity in complex and clinically significant ways.

Together, these articles aim to equip GPs with up-to-date, evidence-based strategies to support patients across the weight spectrum. By broadening the focus beyond lifestyle advice alone, this collection reinforces the role of general practice in delivering effective, compassionate and sustainable care for people living with obesity.

Professor Roger Chen
MBBS, PhD, FRACP, FCSANZ, FESC, FHFA
Professor Chen is Editor-in-Chief of Endocrinology Today, *a Member of the* Medicine Today *Board of Honorary Consultants, a Senior Staff Specialist in the Department of Endocrinology at St Vincent's Hospital and Conjoint Professor at St Vincent's Clinical School, UNSW Sydney, Sydney, NSW.*

CONTENTS PEER REVIEWED

Disclaimer: The following medications are approved by the Therapeutic Goods Administration (TGA) for weight management at the time of publication of this collection: tirzepatide, liraglutide, semaglutide (2.4 mg weekly dose), phentermine, naltrexone/bupropion and orlistat. Eli Lilly does not endorse the use of other medications for weight management outside their approved indications. Please check official prescribing information at https://www.tga.gov.au.



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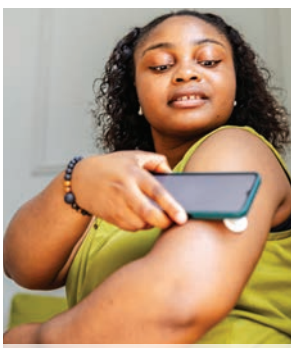

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Managing obesity

Looking beyond lifestyle interventions

ELIZABETH WOOTTON BSc(Hons), MB ChB(Hons), MMed, FRACP
PRIYA SUMITHRAN MB BS(Hons), FRACP, PhD

Most people in Australia are living with overweight or obesity. Obesity and its complications are associated with excess morbidity and mortality, reduced quality of life and substantial financial costs to both individuals and the healthcare system. Effective treatment options for obesity are available, and several promising therapies are currently being investigated in clinical trials.

Key points

- **Almost one in three adults in Australia is living with obesity.**
- **Effective treatments for obesity are available that reduce morbidity and mortality, and improve health and quality of life.**
- **When 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.**

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Obesity increases the risk of ill health and is associated with other conditions, such as type 2 diabetes (T2DM), cardiovascular disease and hypertension. This article outlines current and emerging pharmacological and surgical approaches to the management of obesity.

What is obesity?

Obesity is characterised by 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 commonly used to define obesity, although the BMI alone does not reliably indicate health status and may both under- and overestimate adiposity.[2] Obesity is a complex chronic condition that develops in genetically predisposed individuals in response to several (predominantly environmental) factors.[3]

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 national burden of disease.[4,5] This is due to both its direct health impact and its role in the development of numerous other chronic diseases.

Weight loss can significantly reduce the adverse impact of obesity on health and quality of life; hence, effective treatment is critical (Table 1).[6] A reduction of just 5% in original body weight reduces the

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Dr Wootton is an Endocrinologist and Research Fellow at the Royal Brisbane and Women's Hospital, Brisbane; and Senior Lecturer at the University of Queensland, Brisbane, Qld. Associate Professor Sumithran is an Endocrinologist and Clinical Lead of Obesity Medicine in the Department of Endocrinology and Diabetes, Alfred Health; and Head of the Obesity and Metabolic Medicine Group at the School of Translational Medicine, Monash University, Melbourne, Vic.

Table 1. Expected benefits of weight loss on selected chronic diseases[6]

Diagnosis	Weight loss (%)	Expected benefit of weight loss
Type 2 diabetes	5 to 15	Prevention of diabetes, reductions in glycated haemoglobin levels, decreased need for diabetes medication and potential diabetes remission if duration of diabetes 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

risk of progression to T2DM by more than 50% in people with impaired glucose tolerance, and also improves blood pressure and triglyceride levels.[7] Greater weight loss (10 to 25%) offers progressive benefits, including improvements in the control (and potentially remission) of T2DM, steatotic liver disease, obstructive sleep apnoea, stress urinary incontinence and symptoms of osteoarthritis, as well as improvements in health-associated quality of life.[8] Until recently, most nonsurgical interventions for obesity were expected to achieve sustained weight loss of less than 5%. However, increasingly effective nonsurgical treatments are now becoming available.[9]

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 provides a guide to obesity management in the primary healthcare setting (Box).[6,10]

Specialised obesity services are scarce and often have limited capacity and long waiting times.[11] 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.[12] An update to the National Health and Medical Research Council's clinical practice guidelines for the management of obesity is expected later this year.

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; however, this degree of allied healthcare support is not subsidised by Medicare.[10]

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

The 5 A's framework for obesity management in the primary healthcare setting[6,10]

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 and avoid weight-associated 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

- Use an individualised approach to develop an obesity management program that considers all appropriate options (including lifestyle interventions, pharmacotherapy and bariatric surgery)
- Consider referral to a dietitian and exercise physiologist through a GP Chronic Disease Management plan

Arrange

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

mass). Interactions between biological, psychosocial and 'obesogenic' environmental factors make the maintenance of weight loss challenging for most people.

What pharmacotherapy is available?

Six medications are approved by the TGA for obesity management: liraglutide, semaglutide (2.4 mg weekly dose), tirzepatide, phentermine, naltrexone/bupropion and orlistat (Table 2).[12] Orlistat, liraglutide, naltrexone/bupropion and tirzepatide are indicated for weight management in adults with a BMI 30 kg/m^2 or more, or 27 kg/m^2 to less than 30 kg/m^2 with at least one weight-associated complication. Semaglutide (2.4 mg weekly dose) is indicated for adults with obesity or overweight, and for adolescents aged 12 years and older with obesity and body weight greater than 60 kg. Phentermine is approved for adults and adolescents older than 12 years of age with a BMI of 25 kg/m^2 or higher. Currently, no medications are subsidised by the PBS for obesity management.

The choice of medication requires the consideration of a number of individualised factors, including patient preference, severity of obesity, presence of obesity-related and unrelated medical conditions, and the medication's efficacy, contraindications, adverse effect profile and cost. 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 T2DM, as is dulaglutide (dosage of 1.5 mg weekly). Semaglutide (2.4 mg weekly dose) has an additional indication to reduce the risk of major adverse cardiovascular events in people with established cardiovascular disease and a BMI of 27 km/m^2 or more with or without diabetes. Saxenda, one brand of liraglutide, will be discontinued by the manufacturer at the end of 2025, although generic versions may become available.. In clinical trials for obesity management in people without T2DM, 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.[13,14]

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) T2DM.[14] At doses used to treat T2DM, some GLP-1 receptor agonists (e.g. dulaglutide, liraglutide and semaglutide) reduce mortality and the risk of cardiovascular and renal disease in patients with T2DM.[15] In people with established cardiovascular disease and overweight or obesity but without T2DM, treatment with semaglutide 2.4 mg weekly reduced cardiovascular events (a composite of cardiovascular death, myocardial infarction and stroke) by 20% during 40 months of follow up.[16]

The adverse effects of GLP-1 receptor agonists 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.

Tirzepatide

Tirzepatide is a dual GLP-1 and glucose-dependent insulinotropic polypeptide receptor agonist. It is TGA approved for the treatment of T2DM, obesity and obstructive sleep apnoea, and is administered weekly at dosages of 5 mg, 10 mg or 15 mg. Tirzepatide is the first medication to show a mean weight loss of more than 20% in clinical trials for obesity management. In a phase 3 clinical trial, participants taking tirzepatide at doses of 5 mg, 10 mg and 15 mg achieved mean weight losses of 15%, 20% and 21%, respectively, after 72 weeks of treatment, compared with 3% in the placebo group.[17] In a head-to-head trial over 72 weeks, tirzepatide (10 mg or 15 mg once weekly) resulted in a weight loss of 20%, compared with 14% with semaglutide 2.4 mg once weekly.[18] Adverse effects are predominately gastrointestinal, with a profile similar to that of GLP-1 receptor agonists.

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-associated 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 5 to 10% of initial body weight.[19] 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 an 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).[20]

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 should be considered when prescribing naltrexone/bupropion, particularly those involving cytochrome P450 (CYP) enzyme activity. These include the need to reduce doses of medications metabolised by CYP2D6 (including selective serotonin reuptake

Table 2. Medications for obesity management[12]

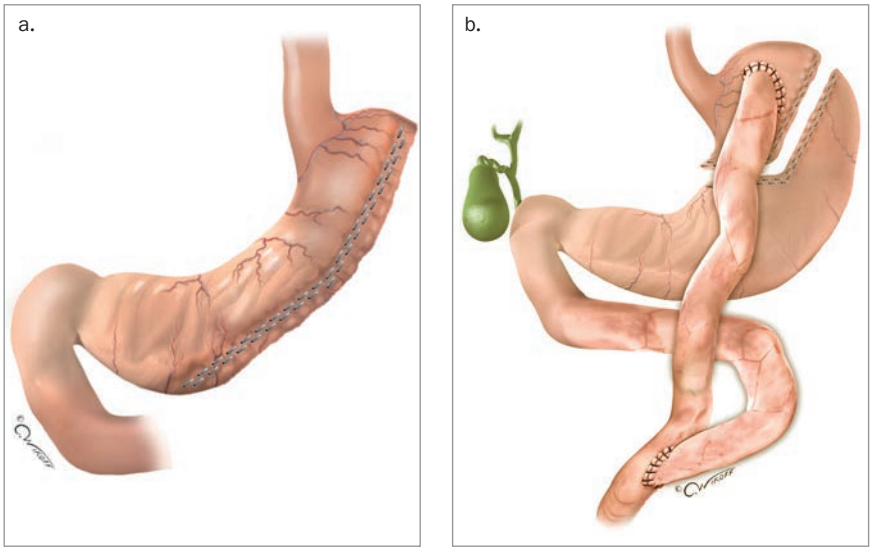
Medication	TGA approved indication	Formulation	Starting dose	Dose escalations and maintenance doses	Maximum dose	Special warnings and precautions for use	Adverse effects	Approximate cost per month†
Liraglutide (Saxenda)	Chronic weight management	Subcutaneous injection	0.6 mg daily	• Increase by 0.6 mg daily per week • Maintenance dose: 3.0 mg	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 (Wegovy)*	Chronic weight management, reduction in risk of major adverse cardiovascular events	Subcutaneous injection	0.25 mg weekly	• Increase to 0.5 mg in weeks 5–8, 1 mg in weeks 9–12 and 1.7 mg in weeks 13–16 • Maintenance dose: 2.4 mg	2.4 mg weekly			$380
Tirzepatide (Mounjaro)*	Chronic weight management, type 2 diabetes, obstructive sleep apnoea	Subcutaneous injection	2.5 mg weekly	• Increase by 2.5 mg every four weeks • Maintenance doses: 5 mg, 10 mg or 15 mg	15 mg weekly			$390 to $690
Phentermine (Duromine, Metermine, Phentermine Juno)	Short-term weight management	15 mg, 30 mg and 40 mg capsules	30 mg daily	• Maintenance dose: 15 mg to 40 mg daily (continuous or intermittent)	40 mg daily	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 (Contrave)	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 (Xenical)	Chronic weight management	120 mg tablets	120 mg three times a day with meals	• N/A	120 mg three times a day with meals	Fat-soluble vitamin deficiency, chronic malabsorption, cholestasis, pregnancy or lactation	Steatorrhoea, oily leakage, excessive flatus, fat-soluble vitamin deficiency	$93
Topiramate (Topamax)‡	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.

* Semaglutide 1 mg (Ozempic) is TGA approved for type 2 diabetes; semaglutide 2.4 mg (Wegovy) is TGA approved for chronic weight management and to reduce the risk of major adverse CV events in people with established CV disease and a BMI of ≥27 kg/m^2 without established type 1 or type 2 diabetes; tirzepatide (Mounjaro) is TGA approved for type 2 diabetes, chronic weight management and obstructive sleep apnoea in patients with obesity.† Cost per month at the recommended dose, estimated from pharmacy websites in February 2025.

‡ Not TGA approved for chronic weight management.

Adapted from the *Australian Obesity Management Algorithm.*[12]



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

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.[21]

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.[21] Common adverse effects include steatorrhoea, oily stools and flatulence. The absorption of fat-soluble vitamins may be reduced by orlistat; therefore, supplementation with a multivitamin should be advised. Orlistat has a weight loss-independent effect on lowering LDL (by 28% compared with lifestyle interventions alone).[22]

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 USA (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 with placebo.[23,24] The adverse effects include gastrointestinal disturbances, difficulty concentrating, paraesthesia, depression, teratogenicity and (rarely) closed-angle glaucoma.

Setmelanotide

Setmelanotide is a melanocortin-4 agonist approved in some parts of the world for the management of obesity caused by rare monogenic variants affecting appetite signalling pathways, including those involving leptin, proprotein convertase subtilisin/kexin type 1 or pro-opiomelanocortin. It is not currently TGA approved.

A separate article in this supplement discusses incretin analogues and other novel agents in development for obesity.

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.[6]

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.[6] 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; 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 limited.[25]

What is the role of metabolic and bariatric surgery?

More than 40,000 individuals are estimated to undergo bariatric surgery each year in Australia.[26] The most common operations are sleeve gastrectomy and Roux-en-Y gastric bypass (RYGB), both of which help achieve substantial, sustained weight loss (Figure 1 and Table 3).[26-29] 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).[27] Substantial weight regain, defined as regain to within 5% of preoperative weight, occurs in fewer than 5% of patients after RYGB and in around 10% of patients after sleeve gastrectomy.[30]

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

- BMI of 40 kg/m^2 or higher
- BMI of 35.0 to 39.9 kg/m^2 and comorbidities that may improve with weight loss
- BMI of 30.0 to 34.9 kg/m^2 with suboptimal control of T2DM and increased risk of cardiovascular disease.[10]

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-associated conditions.[31] Surgery should not be viewed only as a last resort for

Table 3. Advantages and disadvantages of bariatric surgery[27-30]

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

those in whom other obesity treatments have failed. For example, in patients with suboptimal glycaemic control on maximum medical management of T2DM, 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.[32,33]

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.[28,34]

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 than that observed in lifestyle intervention groups after three to six months.[35] Longer-term data are scarce. Reported adverse events include nausea, abdominal pain, deflation and (rarely) gastric perforation. Endoscopic sleeve gastroplasty is another minimally invasive option, in which a suturing device is inserted endoscopically and the stomach is sutured to reduce its size. Similarly, long-term data are lacking, and it is not currently widely available in Australia.

Conclusion

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

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A list of references is included in the online version of this article (https://medicinetoday.com.au/mt/2025/august/supplements/focus-obesity-collection).

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ELIZABETH WOOTTON BSc(Hons), MB ChB(Hons), MMed, FRACP
PRIYA SUMITHRAN MB BS(Hons), FRACP, PhD

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A clinical approach to managing obesity in adults

XI MAY ZHEN MB BS, FRACP
SAMANTHA L. HOCKING MB BS, MMed(Clin Epi), FRACP, PhD

Obesity is a complex chronic disease that is strongly associated with an increased risk of all-cause mortality. Therapies for optimising weight and metabolic health should be guided by an individual's body mass index (with consideration of body composition), comorbidities, and the presence and severity of obesity-associated complications.

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Key Points

- **Obesity is a complex chronic disease associated with increased morbidity and mortality.**
- **Routine screening is required to assess the complications of obesity.**
- **Preconception counselling is crucial as many women are unaware of the potential adverse effects of obesity on both maternal and offspring outcomes.**
- **Even small reductions in body weight can reduce the complications of obesity.**
- **For many individuals, lifestyle interventions alone will not achieve the required amount of weight loss, and pharmacotherapy with or without metabolic surgery should be considered.**

What are the health risks from obesity?

Obesity is a complex chronic disease that is strongly associated with an increased risk of all-cause mortality as well as cardiovascular and cancer mortality.[1-3] Importantly, the longer the duration of obesity, the greater its impact on mortality, which is an important consideration in young adults with obesity.[4]

Excess weight is directly linked to various cardiovascular risk factors.[5] Obesity is associated with an increased risk of various diseases including type 2 diabetes mellitus (T2DM), cardiovascular disease (CVD), chronic kidney disease and metabolic-associated fatty liver disease.[6] The physical burden of carrying excess body weight results in mechanical complications including obstructive sleep apnoea (OSA), urinary incontinence, osteoarthritis and low back pain.[6-8] Obesity is also a state of chronic low-grade inflammation and a major risk factor for at least 13 different types of cancer (Box 1) and dementia.[9,10]

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Dr Zhen is a Staff Specialist and Clinical Lead of the Blacktown Hospital Metabolic Program; Conjoint Senior Lecturer with the School of Medicine, Western Sydney University, Sydney; and an Honorary Visiting Medical Officer at the Department of Endocrinology, Royal Prince Alfred Hospital, Sydney. Associate Professor Hocking is an Endocrinologist at the Department of Endocrinology, Royal Prince Alfred Hospital, Sydney; President of the National Association of Clinical Obesity Services, Sydney; a Member of Council for the Australian New Zealand Obesity Society, Sydney; and a Clinical Academic at the Central Clinical School, Faculty of Medicine and Health, The University of Sydney, Sydney, NSW.

In women of reproductive age, obesity is associated with menstrual disturbance, impairment of oocyte development and quality, anovulation, delayed conception, as well as worsening of the clinical features of polycystic ovary syndrome (PCOS).[11,12] Depression appears to be more common amongst people with obesity compared to those of a healthy weight, although the direction of causality is not clear.[13,14] Women tend to experience more mental health complications associated with obesity than men, which can be exacerbated by discrimination against individuals with a higher body mass index (BMI).[15,16] This can lead to a strong dissatisfaction with one's body weight, shape, or both, which is a risk factor for the development of comorbid disordered eating behaviours.[17,18] The psychological impact of weight stigmatisation can perpetuate weight gain and lead to the development of other chronic diseases.[19]

Why is weight loss important?

Even modest weight loss significantly reduces the complications of obesity. A 5% reduction in total body weight can prevent the development of T2DM in individuals with prediabetes, improve glycaemic control in individuals with T2DM, reduce liver fat, lower systolic blood pressure and triglyceride levels, and improve physical disability amongst patients with knee osteoarthritis.[20-25] Greater weight loss

1. Cancers associated with overweight and obesity

- Endometrial
- Oesophageal adenocarcinoma
- Gastric cardia
- Liver
- Kidney
- Multiple myeloma
- Meningioma
- Pancreatic
- Colon and rectal
- Gallbladder
- Breast (postmenopausal)
- Ovarian
- Thyroid

(≥10%) results in additional health benefits including remission of T2DM, improvements in OSA, reductions in liver inflammation and injury, and a lower risk of cardiovascular events and mortality.[26-30] In women with PCOS, lifestyle interventions improve hyperandrogenism even if weight loss is minimal, although greater weight loss from metabolic surgery also results in improved menstrual regularity and can result in remission.[12,31]

In women with obesity and subfertility, lifestyle interventions have a positive effect on pregnancy and natural conception rates, although the effect on live birth rates remains uncertain.[32] Concerns about the presence of concomitant disordered eating behaviours may caution clinicians against recommending weight management. However, weight management approaches (including medically supervised moderate and severe caloric restriction in combination with behavioural weight loss therapy) do not induce binge eating in overweight adults without pretreatment binge eating, and can reduce binge eating in those with pretreatment binge eating behaviours.[33,34]

When and how do you screen for secondary causes of obesity?

Obesity is a chronic and complex disease influenced by many factors including a genetic predisposition to obesity, work and social environments that promote the consumption of convenient highly processed foods and sedentary behaviour, metabolic adaptations defending against weight loss, as well as other psychosocial and economic drivers.[35] For most individuals, their risk for obesity will be conferred by numerous variants in a number of genetic drivers, that is, polygenic obesity. However, screening for rarer monogenic subtypes of obesity should be considered if extreme obesity occurs at a young age (<5 years of age), particularly when accompanied by clinical features of genetic obesity syndromes (such as extreme hyperphagia), a family history of extreme obesity, or both.[36]

A relatively sudden increase in weight may suggest an endocrine cause for obesity, and screening for causes such as hypothyroidism and Cushing's syndrome (including iatrogenic cortisol excess from exogenous glucocorticoids) should be considered, particularly if suggestive clinical features are present. For instance, if the patient reports dry skin, cold intolerance or other features to suggest hypothyroidism, check the thyroid stimulating hormone level. If there are clinical features of Cushing's syndrome (e.g. easy bruising, facial plethora, proximal myopathy or wide purple striae), measure the midnight salivary cortisol, 24-hour urinary free cortisol, or arrange a 1 mg overnight dexamethasone suppression test (the diagnostic approach will depend on the pretest probability). PCOS should be considered if there are clinical features of insulin resistance (acanthosis nigricans), hyperandrogenism (acne and hirsutism), or oligo-ovulation or anovulation (irregular menstrual cycles).

Review the use of medications associated with weight gain such as antidepressants (e.g. mirtazapine, amitriptyline, sertraline, fluoxetine, paroxetine), antipsychotics (e.g. olanzapine, clozapine, quetiapine, risperidone), anticonvulsants (e.g. valproate, carbamazepine, gabapentin) and treatments for diabetes (e.g. insulin, sulphonylureas, thiazolidinediones), and consider switching to less obesogenic medications if possible.[37] If there is diagnostic uncertainty, consider referral to a specialist service.

How do you assess for obesity-associated complications?

The following routine assessments should be performed in all adults with overweight and obesity:[38]

- weight, height and BMI
- waist circumference
- blood pressure measurement (using an appropriately sized arm cuff)
- assessment of fasting glucose levels (repeated regularly according to local guidelines)[39]
- fasting lipid profile
- liver function tests and screening tools such as calculation of the FIB-4 score (https://liver.org.au/health-professionals/fib-4-calculator/)
- screening for OSA (e.g. STOP-BANG questionnaire)
- screening for depression and anxiety (e.g. K10 screening tool or Patient Health Questionnaire [PHQ]-9)
- screening for disordered eating (e.g. Eating Disorder Examination Questionnaire [EDE-Q])
- screening for CVD (e.g. www.cvdcheck.org.au) for all adults aged 45 years and older (or 30 years and older for Aboriginal and Torres Strait Islander people) without existing CVD or not already known to be at increased risk of CVD
- age-appropriate cancer screening (e.g. bowel, breast, cervix and prostate)
- in women, screening for clinical signs of hyperandrogenism (e.g. hirsutism, acne, male pattern balding).

How do you identify candidates for weight loss interventions?

Treatments for obesity should be guided by an individual's BMI and waist circumference, and the presence and severity of obesity-associated complications. It is imperative that lifestyle modifications are included in the treatment pathway with goals focused on reducing energy intake, optimising diet quality and increasing energy expenditure. Antiobesity pharmacotherapies are indicated for any individual with a BMI of 30 kg/m^2 or more, or a BMI of 27 kg/m^2 or more plus the presence of at least one weight-associated comorbidity (see the case study in Box 2). Consider commencing

2. A young woman with post-traumatic stress disorder and rapid weight gain

Case scenario

A 32-year-old woman presents to her GP because of concerns about her recent rapid weight gain. She reports a weight gain of 15 kg over the past 12 months and has now reached a weight of 98 kg (body mass index 36 kg/m^2). She is frustrated about her inability to control her eating, dislikes how she looks and feels her self-esteem and mood are worsening. This has led to a vicious cycle of comfort eating followed by further weight gain. She admits that she has a 'sweet tooth' and particularly craves chocolate.

She was diagnosed with polycystic ovary syndrome 12 years ago, on the basis of irregular menses and clinical features consistent with hyperandrogenism. She was found to be insulin resistant and was started on metformin 500 mg twice daily. In an attempt to reduce her weight, she tried low carbohydrate, intermittent fasting and 'keto' diets with some success and managed to lose about 5 to 7 kg on each diet. However, each weight loss attempt was followed by weight regain, leading to a gradual increase in her body weight overall.

One year ago, she was diagnosed with post-traumatic stress disorder (PTSD) after experiencing years of bullying at work. She was started on sertraline 100 mg daily and has been regularly seeing a psychologist. Since starting sertraline, her weight has increased rapidly despite engaging with a dietitian and exercise physiologist using a chronic disease management plan. She is keen to explore additional therapies to assist with weight loss.

Treatment strategies

Weight optimisation in this case requires a sensitive approach to avoid provoking feelings of weight stigma or bias. This woman has reported frustration at an inability to control her eating, a vicious cycle of 'comfort' eating, followed by further weight gain, poor body image and worsening self-esteem and mood. She has also already engaged in attempts to reduce her weight. If she was to continue unsupervised food restriction or food elimination, this could not only leave her vulnerable to the development of disordered eating but could actively jeopardise her ability to develop lifestyle modifications that support healthy weight regulation and the reduction of eating as a means of emotion regulation.

A detailed review of her dietary and exercise patterns is crucial. The ongoing rapid weight gain suggests that there is suboptimal adherence to lifestyle recommendations, and the reasons underlying this need to be explored so that appropriate interventions can be initiated and support provided. In addition to her diagnosis of PTSD, she may also be vulnerable to the development of disordered eating behaviours and a mood disorder. She requires a multidisciplinary approach to weight management including medical, dietetic and psychological input to facilitate supervised weight loss and the development of healthy lifestyle and eating behaviours. A mental health treatment plan with referral to a psychologist is required to address weight loss expectations and body image dissatisfaction, with body acceptance necessary to reduce the likelihood of behaviours that may perpetuate disordered eating (particularly if her weight stabilises higher than expected). Nonpharmacological treatment for her PTSD could also be explored.

The use of sertraline should be reviewed with referral to psychiatry, if needed. Weight loss pharmacotherapy is likely required in this situation to help suppress her appetite and food cravings, and to promote sustained weight loss. In this clinical scenario, a glucagon-like peptide 1 (GLP-1) receptor agonist or dual glucose-dependent insulinotropic polypeptide/GLP-1 receptor agonist would be the most appropriate pharmacotherapy given her insulin resistance and mood disorder. It would be prudent for clinicians to monitor patients for any mood changes during treatment with these agents. Her current use of a selective serotonin reuptake inhibitor is a precaution to the use of phentermine and naltrexone/bupropion, as the use of these agents may have an adverse effect on her mood. Pharmacotherapy should be prescribed in addition to ongoing dietetic support to achieve a balanced and nutritionally complete reduced energy diet and regular physical activity.

antiobesity pharmacotherapies when lifestyle modifications alone have been unsuccessful in achieving desired weight loss, or to maintain weight loss and prevent weight regain. Metabolic surgery should be considered for adults with a BMI of 40 kg/m^2 or more, or a BMI of 30.0 to 39.9 kg/m^2 with comorbidities that may improve with weight loss.

Special considerations in women of childbearing age

Many women planning to conceive are unaware of the potential adverse effects of obesity on both maternal and offspring outcomes. Obesity is associated with reduced fertility and oocyte quality, and also adversely impacts the quality and early development of the embryo.[40,41] Obesity is associated with increased risks in the antenatal, intrapartum and postpartum periods, as well as increased anaesthetic risk.[42] There is a direct relationship between the class of obesity and the likelihood of serious adverse outcomes.[42] A large retrospective cohort study found that when compared with normal-weight women, the hazard ratio for stillbirth was 1.36 for overweight women, 1.71 for women with class I obesity, 2.00 for women with class II obesity, 2.48 for women with class III obesity and 3.16 for women with a BMI of 50 kg/m^2 and above.[43] Perinatal exposure to maternal obesity is also associated with cardiometabolic morbidity in the offspring.[44,45]

Height, weight and BMI should be measured at preconception appointments. The risks of overweight and obesity on fertility and pregnancy outcomes need to be discussed using a sensitive and person-centred approach. The Royal Australian and New Zealand College of Obstetricians and Gynaecologists *Management of Obesity in Pregnancy Best Practice Statement* recommends starting folic acid 5 mg daily (due to the increased risk of neural tube defects) and iodine 150 mcg daily (unless contraindicated) in the preconception period for women with obesity.[46]

Ideally, weight and metabolic health should be optimised prior to conception to reduce the risk of pregnancy-associated complications and to minimise exposure of the foetus to an adverse metabolic environment. A multifaceted and holistic approach to weight management is best provided by an experienced healthcare team. At present, there is a lack of conclusive randomised trial data regarding the optimal weight loss interventions for pre-pregnancy use.[46]

Table. Summary of medications with TGA approval for weight loss[52,54,62-72]

	Phentermine (Duromine, Metermine, Phentermine Juno)	Naltrexone/buproprion (Contrave)	Orlistat (Xenical)	Liraglutide (Saxenda) and semaglutide (Wegovy)*	Tirzapatide (Mounjaro)*
Formulation	Oral tablet			Subcutaneous injection	
Mechanism of action	Sympathomimetic action resulting in decreased food intake and increased resting energy expenditure	Potentially modulates food cravings and mood via hypothalamic melanocortin system as well as brain reward systems[62,63]	Inhibits pancreatic and gastric lipase, resulting in reduced fat absorption	GLP-1 RAs (liraglutide and semaglutide) and GIP/GLP-1 RAs (tirzepatide) increase glucose-dependent insulin secretion, decrease inappropriate glucagon secretion, slow gastric emptying and regulate food-associated behaviours, resulting in decreased appetite as well as increased postprandial satiety and fullness. The dual agonism of tirzepatide, at GIP and GLP-1 receptors, provides additional mechanisms of action which are likely more effective at countering the complex pathways involved in achieving and maintaining weight loss.[64,65] GIP and GLP-1 have both overlapping and nonoverlapping expression and function.[66-68] Furthermore, adipocytes lack functional GLP-1 receptors but have functional GIP receptors that may play a role in the direct regulation of adipocytes by tirzepatide[69,70]	
Special warnings and precautions for use	• Uncontrolled hypertension • Cardiac disease • Hyperthyroidism • Glaucoma • Pregnancy • Breastfeeding • Previous drug abuse • Use of MAOIs, SSRIs	• Uncontrolled hypertension • History of seizures • Known central nervous system tumours • Chronic opioid or opiate agonist/partial agonist use, or acute opiate withdrawal • Abrupt discontinuation of alcohol, benzodiazepines, barbiturates or antiepileptic drugs • Anorexia nervosa or bulimia • Pregnancy • Breastfeeding • Severe hepatic or renal impairment • Use within 14 days of treatment with MAOIs	• Anorexia • Fat-soluble vitamin deficiency • Malabsorption • Cholestasis • Pregnancy • Breastfeeding • Patients with or at risk of oxalate nephropathy	• Pregnancy • Breastfeeding • History of pancreatitis (particularly when the inciting cause has not been removed) • Personal or family history of medullary thyroid cancer or multiple endocrine neoplasia 2A or 2B	

Abbreviations: GLP-1 RA = glucagon-like peptide 1 receptor agonist; GIP/GLP-1 RA = dual glucose-dependent insulinotropic polypeptide/glucagon-like peptide 1 receptor agonist; GLP-1 = glucagon-like peptide 1; GIP = glucose-dependent insulinotropic polypeptide; MAOI = monoamine oxidase inhibitor; SSRI = selective serotonin reuptake inhibitor; T2DM = type 2 diabetes mellitus.
* Semaglutide 1 mg (Ozempic) is TGA approved for type 2 diabetes; semaglutide 2.4 mg (Wegovy) is TGA approved for chronic weight management and to reduce the risk of major adverse CV events in people with established CV disease and a BMI of ≥27 kg/m^2 without established type 1 or type 2 diabetes; tirzepatide (Mounjaro) is TGA approved for type 2 diabetes, chronic weight management and obstructive sleep apnoea in patients with obesity.

Women should be advised to use reliable forms of contraception while working on weight loss, particularly when using antiobesity pharmacotherapy. Medications for weight loss should be avoided during the time of conception, during pregnancy and while breastfeeding for safety reasons. Usually, antiobesity pharmacotherapy should be ceased for a period of at least six weeks prior to attempting to conceive (the time period will vary depending on the agent used); the manufacturers of semaglutide have indicated that this agent should be discontinued at least two months before a planned pregnancy due to the medication's long half-life.[47]

Women who have undergone metabolic surgery require additional nutritional supplementation and careful monitoring for micronutrient deficiencies in the preconception period. It is recommended that conception is avoided for 12 to 18 months following metabolic surgery, particularly when there is rapid weight loss or nutritional deficiencies.[48]

Table. Summary of medications with TGA approval for weight loss[52,54,62-72] *continued*

	Phentermine (Duromine, Metermine, Phentermine Juno)	Naltrexone/buproprion (Contrave)	Orlistat (Xenical)	Liraglutide (Saxenda) and semaglutide (Wegovy)*	Tirzapatide (Mounjaro)*
Adverse effects	• Hypertension • Tachycardia • Insomnia • Restlessness • Dry mouth • Constipation or diarrhoea	• Nausea or vomiting • Constipation • Dizziness • Hypertension • Tachycardia • Headaches • Insomnia • Dry mouth • Word finding difficulty • Neuropsychiatric adverse events • Seizures • Angle-closure glaucoma in a patient with anatomically narrow angles who does not have a patent iridectomy	• Steatorrhoea • Excessive flatus with or without discharge • Fat-soluble vitamin deficiency • Oxalate-induced acute kidney injury	• Nausea or vomiting • Diarrhoea • Constipation • Pancreatitis • Gallstones • Cholecystitis • Potential increased risk of medullary thyroid cancer	
Other considerations	Approved for short-term use (12 weeks), subject to periodic medical review	Useful option for those also aiming for alcohol or smoking cessation	Orlistat markedly decreases blood cyclosporin concentrations. Warfarin doses may need to be reduced due to reduced absorption of vitamin K. Coprescribing with psyllium may reduce the gastrointestinal side effects of orlistat	Saxenda, one brand of liraglutide, will be discontinued by the manufacturer at the end of 2025. Semaglutide is currently available in two forms: • Ozempic: PBS subsidised for people with T2DM meeting criteria, but not TGA approved for weight management • Wegovy: TGA approved for adults as an adjunct to lifestyle modification for chronic weight management and as an adjunct to standard of care therapy to reduce the risk of major adverse cardiovascular events The SELECT trial demonstrated that subcutaneous semaglutide at a dose of 2.4 mg weekly was superior to placebo in reducing the incidence of death from cardiovascular causes, nonfatal myocardial infarction or nonfatal stroke at a mean follow up of 39.8 months in patients with pre-existing cardiovascular disease and overweight or obesity but without diabetes[54]	The SURMOUNT-5 trial showed that, among people with obesity (but without diabetes), treatment with tirzepatide 10 or 15 mg weekly was superior to semaglutide 1.7 or 2.4 mg weekly with regard to body weight and waist circumference reduction at week 72[64]

Abbreviations: GLP-1 RA = glucagon-like peptide 1 receptor agonist; GIP/GLP-1 RA = dual glucose-dependent insulinotropic polypeptide/glucagon-like peptide 1 receptor agonist; GLP-1 = glucagon-like peptide 1; GIP = glucose-dependent insulinotropic polypeptide; MAOI = monoamine oxidase inhibitor; SSRI = selective serotonin reuptake inhibitor; T2DM = type 2 diabetes mellitus.
* Semaglutide 1 mg (Ozempic) is TGA approved for type 2 diabetes; semaglutide 2.4 mg (Wegovy) is TGA approved for chronic weight management and to reduce the risk of major adverse CV events in people with established CV disease and a BMI of ≥27 kg/m^2 without established type 1 or type 2 diabetes; tirzepatide (Mounjaro) is TGA approved for type 2 diabetes, chronic weight management and obstructive sleep apnoea in patients with obesity.

Overview of lifestyle interventions and the role of behaviour therapy

Lifestyle interventions to reduce energy intake, increase energy expenditure and improve nutritional quality are the cornerstone of weight management. A network of experienced clinicians providing support and supervision is key to the success of lifestyle interventions. Please refer to the *Australian Dietary Guidelines* and the *Australian Guide to Healthy Eating* for general dietary advice.[49,50] Involving an experienced multidisciplinary team (including an accredited practicing dietitian and exercise physiologist) is helpful

and creates a network of support around the patient. Behaviour therapy is key to helping people make long-term changes in the way they respond to stimuli that trigger eating. Behaviour modification programs offered by psychologists and other suitably experienced clinicians can result in more weight loss and less weight regain.[51] If there is any concern for a binge eating disorder, consider referral to a health practitioner with expertise in eating disorders.

Options for reducing energy intake include:

- Reduced Energy Diet (RED): modest energy deficit of 2000 to 4000 kJ/day (energy deficit of 480 to 960 kcal/day)
- Low Energy Diet (LED): aim to reduce total daily energy intake to 4200 to 5000 kJ (1000 to 1200 kcal/day)
- Very Low Energy Diet (VLED): aim to reduce energy intake to less than 3300 kJ/day (800 kcal/day) by substituting meals with formulated meal replacements. Medical supervision and regular clinical review are helpful when using VLEDs, as there are contraindications and precautions.

Those with a BMI of 30 to 39.9 kg/m^2 and no obesity-associated complications could trial RED or LED initially, and then consider VLED if weight loss is inadequate.[52] People with a BMI of 30 to 39.9 kg/m^2 and obesity-associated complications, and those with a BMI of 40 kg/m^2 and above should generally commence VLED directly.[52] Please refer to the latest *Australian Obesity Management Algorithm* for further details such as contraindications to VLED, and the use of VLED in special groups (e.g. chronic kidney disease, people with diabetes and those using sodium-glucose cotransporter-2 inhibitors or warfarin).[52]

Regular physical activity is a key component of weight management and exercise programs should be titrated to individual needs. For instance, people with musculoskeletal problems may benefit from choosing aquatic activities, and those with cardiovascular or respiratory diseases will likely require a gentler program as tolerated. An exercise physiologist will be able to provide tailored advice on suitable exercise programs for the patient. For general advice on physical activity, please refer to the *Physical Activity and Exercise Guidelines* produced by the Australian Government.[53]

What are the pharmacotherapies available for weight loss?

At present, phentermine, naltrexone/buproprion, orlistat, liraglutide, semaglutide (2.4 mg weekly dose) and tirzepatide are approved by the TGA for chronic weight management. Semaglutide (2.4 mg weekly dose) is also is approved by the TGA as an adjunct to standard-of-care therapy to reduce the risk of major adverse cardiovascular events (cardiovascular death, nonfatal myocardial infarction or nonfatal stroke) in adults with established cardiovascular disease, with a BMI of 27 kg/m^2 and above, and without established type 1 or type 2 diabetes. Topiramate and phentermine-topiramate are frequently used off-label for weight management but are not currently approved by the TGA for this indication.

The choice of pharmacotherapy should be based on a careful assessment of factors such as patient age, comorbidities (e.g. diabetes as well as cardiovascular, chronic kidney or liver diseases), medication side effect profiles and patient preference. For instance, among those with pre-existing cardiovascular disease and overweight or obesity (but without diabetes), subcutaneous semaglutide 2.4 mg weekly was superior to placebo in reducing the incidence of nonfatal myocardial infarction, death from cardiovascular causes or nonfatal stroke (mean follow-up period was 39.8 months).[54] Semaglutide 2.4 mg once weekly has also been shown to significantly improve pain associated with knee osteoarthritis and to improve symptoms and physical limitations in individuals with obesity and heart failure with preserved ejection fraction.[55,56] In adults with metabolic dysfunction-associated steatohepatitis (MASH) and moderate or advanced liver fibrosis, subcutaneous semaglutide 2.4 mg weekly was shown to result in higher rates of steatohepatitis resolution and greater reduction in liver fibrosis when compared to placebo at interim analysis after 72 weeks of treatment.[57] Similarly, in adults with MASH and moderate or severe fibrosis, tirzepatide (5 mg, 10 mg or 15 mg) for 52 weeks was more effective than placebo in achieving resolution of MASH without worsening of fibrosis.[58]

Tirzepatide has been shown to reduce OSA severity when compared to placebo in adults with OSA and obesity, as well as reduce cardiovascular death and worsening heart failure in people with obesity and heart failure with preserved ejection fraction.[59,60]

Regular monitoring while on antiobesity pharmacotherapy is crucial to monitor progress and ensure safety. If patients are unable to lose at least 5% of total body weight after 12 to 24 weeks of treatment on the maximum dose of the chosen antiobesity agent, it is important to review medication adherence and individual circumstances, and consider whether a trial of an alternative medication is appropriate.

Certain patient groups require close monitoring on antiobesity pharmacotherapy. For instance, those with diabetes on glucose-lowering therapy (especially insulin, sulphonylureas or both) require close monitoring of blood glucose levels to avoid hypoglycaemia. Similarly, patients with hypertension require regular blood pressure monitoring with down-titration of antihypertensive therapy as appropriate.

Abrupt discontinuation of antiobesity pharmacotherapy is associated with weight regain and recurrence of weight-associated comorbidities in most cases. For instance, at one year following cessation of semaglutide 2.4 mg once weekly and lifestyle interventions (administered for 68 weeks, including 16 weeks of semaglutide dose escalation), participants in the STEP 1 trial extension regained two-thirds of their prior weight loss. Cardiometabolic improvements observed during treatment (from week zero to week 68) also reverted towards baseline after one year of therapy withdrawal.[61]

A summary of all the TGA approved medications for weight loss is shown in the Table.[52,54,62-72]

Overview of metabolic surgery

For individuals with obesity-associated complications, a high BMI or for those in whom lifestyle and pharmacotherapy have not resulted

in the required weight loss, metabolic surgery may be considered as part of a comprehensive treatment plan. The potential benefits of metabolic surgery should be carefully weighed against the individual's risk profile, and a thorough evaluation of mental health and psychosocial factors is critical. Surgery should ideally be performed at high-volume centres with experienced multidisciplinary teams. After metabolic surgery, patients will require long-term monitoring of micronutrient and nutritional status, as well as ongoing review of lifestyle and psychological factors.

The Second Diabetes Surgery Summit, held in 2016 and endorsed by the Australian Diabetes Society, produced guidelines that state that metabolic surgery is recommended for individuals with:

- a BMI of 40 kg/m^2 and above, regardless of the level of glycaemic control or complexity of glucose-lowering regimens
- a BMI of 35.0 to 39.9 kg/m^2, with inadequate glycaemic management despite lifestyle and optimal medical therapy.[73]

The American Society for Metabolic and Bariatric Surgery and International Federation for the Surgery of Obesity and Metabolic Disorders *Indications for Metabolic and Bariatric Surgery 2022* state that metabolic and bariatric surgery should be:

- recommended for individuals with a BMI of 35 kg/m^2 and above, regardless of presence, absence or severity of comorbidities
- considered for individuals with metabolic disease and a BMI of 30 to 34.9 kg/m^2
- offered to individuals in the Asian population with a BMI of 27.5 kg/m^2 and above, noting that a BMI of 25 kg/m^2 and above in this group suggests clinical obesity.[74]

The American Diabetes Association Standards of Medical Care in Diabetes (2025) recommend that metabolic surgery be considered as a weight and glycaemic management option in people with diabetes with a BMI of 30.0 kg/m^2 and above (or ≥27.5 kg/m^2 in Asian American individuals) who are otherwise good surgical candidates.[75]

Ethnicities such as South Asian, East Asian, Southeast Asian and Australian Aboriginal and Torres Straight Islanders have been shown to have higher adiposity and diabetes risk at a given BMI.[52,76-79] The *Australian Obesity Management Algorithm* (updated July 2024) reflects this by adopting lower BMI thresholds for these populations: a BMI of 27.5 to 37.4 kg/m^2 is equivalent to a BMI of 30 to 39.9 kg/m^2, and a BMI of 37.5 kg/m^2 and above is equivalent to a BMI of 40 kg/m^2 and above.[52]

Summary

Therapies for managing obesity should be guided by an individual's BMI (with consideration of body composition), comorbidities and the presence and severity of obesity-associated complications. A network of experienced clinicians providing support and supervision is crucial to the success of lifestyle interventions. Lifestyle modification, pharmacotherapy and metabolic surgery should be considered as part of a comprehensive treatment plan. **ET**

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A list of references is included in the online version of this article (https://medicinetoday.com.au/mt/2025/august/supplements/focus-obesity-collection).

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A clinical approach to managing obesity in adults

XI MAY ZHEN MB BS, FRACP
SAMANTHA L. HOCKING MB BS, MMed(Clin Epi), FRACP, PhD

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New pharmacological treatments for obesity

Incretin analogues, their mechanism of action, efficacy and safety

TANIA P. MARKOVIC MB BS, PhD, FRACP
SAMANTHA L. HOCKING MB BS, MMed(Clin Epi), FRACP, PhD

Incretin analogues are very effective weight loss medications resulting in weight loss approaching that achieved with bariatric surgery. They also have cardiovascular benefits. However, these treatments are costly and their availability has been limited because of overdemand.

KEY POINTS

- Obesity increases the risk of disease, including serious cardiometabolic disease.
- Incretin analogue treatment results in weight loss with a substantial reduction in cardiovascular risk factors. The newer agents have been associated with weight loss of 15 to 20% of bodyweight, which approaches that seen with bariatric surgery.
- For the first time, a pharmacological obesity treatment, semaglutide (at a weekly dose of 2.4 mg), has been shown to reduce major adverse cardiovascular events in people with obesity and established cardiovascular disease.
- Incretin analogues also show beneficial effects in heart failure, peripheral vascular disease, renal disease, obstructive sleep apnoea and metabolic dysfunction-associated steatohepatitis and have potential neuroprotective properties.
- Incretin analogues are an increasingly important class of drugs that provide substantial health benefits for people with obesity, with adverse effects limited primarily to gastrointestinal disturbances. Equity of access is a problem because these medications are costly and there have been global shortages because of overdemand.

Obesity and its associated medical complications are a major problem in Australia and worldwide. In 2022 to 2023, 26.4% of children and adolescents aged 2 to 17 years and 65.8% of adults (aged 18 years and above) in Australia were classified as having overweight or obesity.[1] Obesity increases the risk of disease, including serious cardiometabolic disease, and prevention is key, as sustained long-term weight loss is rare once obesity is established.

Bariatric surgery was previously the most effective and durable weight-loss intervention for obesity and has been associated with excellent health outcomes. Incretin-based pharmacotherapy now offers a medical alternative, resulting in a 15 to 20% body weight loss – close to that achieved with

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Associate Professor Markovic is Director of the Metabolism & Obesity Service at Royal Prince Alfred Hospital, Sydney; and Clinical Associate Professor at the Boden Initiative, Charles Perkins Centre and Central Clinical School, Faculty of Medicine and Health, The University of Sydney, Sydney. Associate Professor Hocking is a Clinical Academic at the Department of Endocrinology, Royal Prince Alfred Hospital, Sydney; and at the Boden Initiative, Charles Perkins Centre and Central Clinical School, Faculty of Medicine and Health, The University of Sydney, Sydney, NSW.

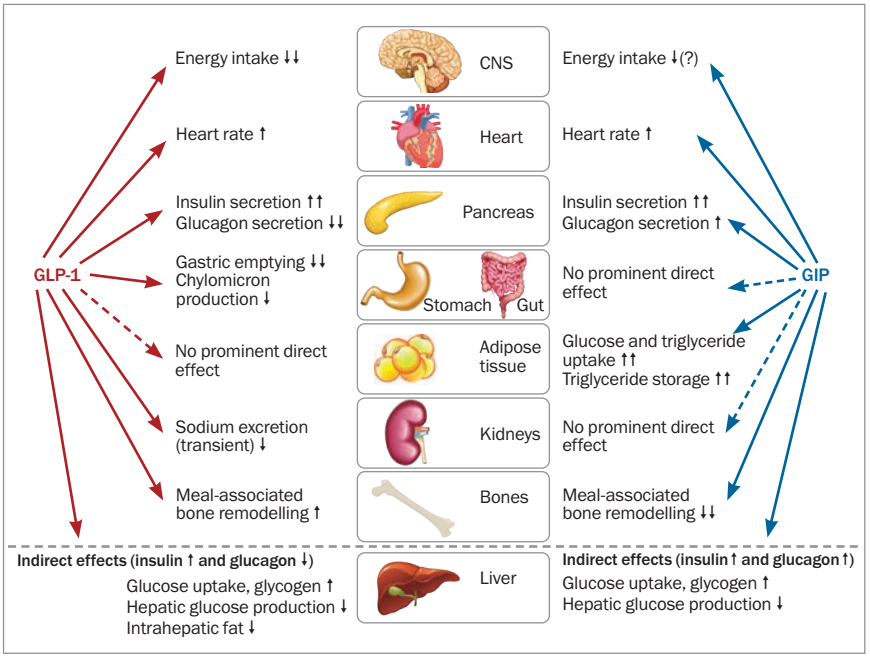

Figure. Biological effects of glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptor agonists at the tissue level.
Key: ↑ = increased; ↑↑ = marked increase; ↓ = decreased; ↓↓ = marked decrease.
Adapted from Nauck MA, et al. Diabetes Obes Metab 2021; 23 Suppl 3: 5-29.[3]

bariatric surgery – and providing considerable cardiovascular benefit. Weight loss is sustained while patients remain on incretin treatment. However, these treatments are costly and their popularity has resulted in shortages, creating stress and uncertainty for people with obesity.

What are incretins and how do they result in weight loss?

Incretins are hormones produced in the gastrointestinal tract that are rapidly secreted in response to a meal. They communicate nutrient intake to systems that regulate postprandial homeostasis, including the stimulation of pancreatic insulin release in a glucose-dependent manner. This is known as the incretin effect, and it occurs after oral but not intravenous administration of glucose. In addition, incretins regulate gastric motility, nutrient absorption, blood flow and food intake.[2] The two dominant incretins are glucagon-like peptide-1 (GLP-1), secreted by enteroendocrine L cells (located in the ileum and colon), and glucose-dependent insulinotropic peptide (GIP), secreted by K cells (located mainly in the duodenum). These hormones are rapidly degraded by dipeptidyl peptidase-4 and neutral endopeptidase 24.11, with renal clearance resulting in a short half-life of two minutes.[3] GLP-1 is also produced in cerebral preproglucagon neurons, where it is released locally and acts as a neurotransmitter. Peripheral and central GLP-1 systems appear to be separate and act independently.[4]

Of the two dominant incretins, GIP has been shown to have a greater effect on insulin release following oral glucose ingestion in healthy humans. At euglycaemia or hyperglycaemia, GLP-1 suppresses glucagon secretion. When blood glucose levels are 5 mmol/L or less, GLP-1 has no effect, and may even increase glucagon secretion. In contrast, GIP stimulates glucagon secretion, with enhanced activity at lower glycaemic levels.

GLP-1 and GIP receptors are widespread in humans with abundant levels in pancreatic beta and, to a lesser degree, alpha cells. They have also been found in subcutaneous and visceral adipose tissue, as well as the heart, lungs, kidneys, blood vessels, bone and the gastrointestinal tract. In rodents and nonhuman primates, receptors have also been found in brain tissue involved in appetite regulation, satiety, energy intake and expenditure (i.e. hypothalamus and brain stem nuclei), as well as regions involved in synaptic plasticity, memory, reward functions and emotional responses (Figure).[3]

Effects of incretins on the gastrointestinal tract

Gut-released GLP-1 acts as a hormone and binds primarily to receptors in the gastrointestinal system. It also acts on vagal afferent neurons that signal the brain on gut nutrient status. Physiological and pharmacological doses of GLP-1 slow gastric emptying, but GIP has no such effect. Although tachyphylaxis to this effect may occur with long-acting GLP-1 receptor agonists, GLP-1-associated slowing of gastric emptying does not appear to be responsible for the nausea and vomiting often reported with the use of GLP-1 receptor agonist treatment. High doses of GLP-1 receptor agonist resulting in complete cessation of gastric emptying are not usually associated with gastrointestinal symptoms, which appear to be centrally mediated.[3]

In slowing gastric emptying, gastric acid and pancreatic exocrine secretion are also reduced by GLP-1. GLP-1 and GLP-1 receptor agonists also reduce intestinal motility and this may affect nutrient absorption. These effects have been referred to as the 'ileal brake', which signals the body to stop eating and cease digestion and nutrient absorption. This may contribute to the diarrhoea sometimes reported with GLP-1 receptor agonist treatment.

Energy intake and expenditure

Physiological plasma levels of GLP-1 and GIP do not affect appetite. However, at pharmacological concentrations, GLP-1 and possibly GIP reduce appetite and

prospective food intake, and increase satiety.[5] GLP-1 receptor agonists can stimulate GLP-1 receptors in the area postrema, a circumventricular organ in the lower brainstem that has fenestrated capillaries and can sense hormonal signals in the general circulation, and appetite centres in the hypothalamus, which have fenestrated capillaries in the median eminence. The area postrema is responsible for emesis and nausea and is likely the main contributor to these GLP-1 receptor agonist-associated side effects. Peripherally administered liraglutide is taken up by the hypothalamus (arcuate and paraventricular nuclei) where it stimulates pro-opiomelanocortin and amphetamine-regulated transcript to reduce appetite and induce weight loss.[6] However, GLP-1 receptor agonists and gut-derived GLP-1 do not cross the blood–brain barrier and cannot access GLP-1 receptors in the brain parenchyma, which can only be accessed by brain (pre-proglucagon neuron)-derived GLP-1.[4] Paradoxically, GIP-receptor knockout mice studies showed that, when fed a high-fat diet, the mice were resistant to weight gain.[4]

Based on animal studies, it has been suggested that antagonism of the GIP receptor may enhance GLP-1 receptor activity, whereas chronic GIP-receptor agonism may desensitise GIP-receptor activity mimicking antagonism.[2] However, other animal studies suggest central GIP-receptor stimulation reduces food intake and body weight.[7] At physiological or pharmacological doses, GLP-1 has not been shown to affect energy expenditure.[3] However, at pharmacological doses, GIP agonism appears to increase fat oxidation by promoting futile calcium cycling, thereby diminishing the metabolic adaptation often observed with weight loss.[8,9]

Incretin therapies currently available in Australia

Dulaglutide, liraglutide and semaglutide – synthetic versions of human GLP-1 – and tirzepatide, a single-molecule dual GLP-1 and GIP receptor coagonist, are available in Australia. Liraglutide, semaglutide (2.4 mg weekly dose) and tirzepatide have been trialled for the management of obesity. Although dulaglutide has not been studied as an obesity treatment, it results in modest weight loss in people with type 2 diabetes, with head-to-head trials showing it to be less effective than liraglutide 1.8 mg, semaglutide 1.0 mg and tirzepatide.[10-12]

In Australia, liraglutide, semaglutide (2.4 mg weekly dose) and tirzepatide are TGA approved for weight management in adults. Saxenda, one brand of liraglutide, will be discontinued by the manufacturer at the end of 2025. Semaglutide (2.4 mg weekly dose) is also approved for use in adolescents aged 12 years and older with obesity. All these medications are administered by subcutaneous injection into the abdomen, upper arm or thigh. Their dosing, weight loss efficacy and cost are summarised in the Table.[11,13-25] As with other weight loss treatments, people with type 2 diabetes tend to lose less weight than those without type 2 diabetes.[15-18] These agents appear to be equally effective in patients who have undergone bariatric surgery.[26]

Body composition changes

Incretin analogues produce substantial weight loss approaching that achieved with bariatric surgery. Weight loss inevitably involves loss of both adipose tissue and lean tissue. However, treatment with these agents results in relatively greater fat loss, including visceral fat reduction, leading to an increased proportion of lean mass to total body mass.[16,27]

Efficacy in children and adolescents

Liraglutide 3 mg daily for one year was well tolerated in adolescents with obesity and resulted in a 4.6% reduction in body mass index (BMI) compared with placebo.[28] In children aged six to 12 years with nonsyndromic obesity, liraglutide 3 mg daily for one year produced a 7.4% reduction in BMI compared with placebo.[29] In adolescents with obesity, semaglutide 2.4 mg once weekly led to weight loss similar to that observed in adults (a 16.1% mean reduction in BMI from baseline *vs* 0.6% with placebo at 68 weeks), along with improvements in cardiometabolic risk factors such as waist circumference, glycated haemoglobin (HbA_{1c}), LDL-cholesterol, triglyceride and alanine transaminase levels.[30]

What dose should be used?

For glycaemic control in people with type 2 diabetes, liraglutide doses above 1.8 mg once daily provide no substantial additional benefit. Similarly, semaglutide doses above 1 mg once weekly have a negligible effect on glycaemic control in most people with type 2 diabetes. However, tirzepatide demonstrates a dose-dependent effect on glycaemia: at 5 mg once weekly, 27% of people with type 2 diabetes achieved an HbA_{1c} below 5.7%, compared with 46% at 15 mg once weekly.[15] Although high doses generally result in greater weight loss, the incremental benefit diminishes beyond 10 mg once weekly.

The recommended dose of liraglutide for the management of type 2 diabetes is 1.2 to 1.8 mg daily, whereas the dose for weight loss is 3 mg daily. For semaglutide, the dose for type 2 diabetes is 1 mg once weekly, compared with 2.4 mg once weekly for weight loss. Tirzepatide's maximum weekly dose is 15 mg for both type 2 diabetes and obesity. Clinically, many patients do not require the maximum recommended dose to achieve satisfactory weight loss. We recommend titrating the dose of an incretin analogue to the level required for adequate appetite control and weight loss, increasing only after the current dose is well tolerated. If a patient is experiencing side effects, dose escalation should be slower, and if severe, the dose should be reduced back to the dose that was tolerated. Patients should maintain that dose for about one month before attempting to increase the dose again.

How long should these medications be used?

Weight regain occurs when incretin analogues are discontinued. This was well demonstrated in a trial where participants

TABLE. TGA STATUS, DOSES, WEIGHT-LOSS DATA AND COST OF INCRETIN THERAPIES[11,13-25]

	Dulaglutide (Trulicity)	Liraglutide (Victoza)	Liraglutide (Saxenda)	Semaglutide (Ozempic)*	Semaglutide (Wegovy)*	Tirzepatide (Mounjaro)*
TGA status	Approved for T2D	Approved for T2D	Approved for obesity	Approved for T2D	Approved for obesity and reduction in the risk of major adverse cardiovascular events	Approved for T2D, obesity and obstructive sleep apnoea
Doses	1.5 mg		0.6, 1.2, 1.8, 2.4, 3.0 mg	0.25, 0.5, 1.0 mg	0.25, 0.5, 1.0, 1.7, 2.4 mg	2.5, 5, 7.5, 10, 12.5, 15 mg
Starting dose	1.5 mg weekly	0.6 mg daily	0.6 mg daily	0.25 mg once weekly	0.25 mg once weekly	2.5 mg once weekly
Recommended dose	1.5 mg weekly	1.2 to 1.8 mg daily	3.0 mg daily	1.0 mg once weekly	2.4 mg once weekly	5 to 15 mg once weekly
Dose titration	Nil	Weekly	4 weekly	4 weekly	4 weekly	4 weekly
Weight loss at 1 year	In T2D −3 kg *vs* −6.5 kg semaglutide 1 mg[11]	In T2D −2.0 to −2.5 kg *vs* +1.25 kg glimepiride[13]	In obesity 8.0% *vs* 2.6% placebo[14]	In T2D 6.7%[15]	In obesity 14.9% *vs* 2.4% placebo[16] In T2D 9.6% *vs* 3.4% placebo[17]	In obesity 15.0% 5 mg, 19.5% 10 mg, 20.9% 15 mg *vs* 3.1% placebo[18] In T2D 8.5% 5 mg, 11.0% 10 mg, 13.1% 15 mg[15]
Longer-term effect on weight	In T2D −2.88 kg at 104 weeks[19]		In obesity 6.1% *vs* 1.9% placebo at 3 years[20]		In obesity 15.2% *vs* 2.6% placebo at 2 years[21] 10.1% *vs* 0.4% placebo at 4.25 years[22]	In obesity 20.2% with tirzepatide *vs* 13.7% with semaglutide (2.4 mg weekly dose) at 72 weeks[23] In obesity 12.3% 5 mg, 18.7% 10 mg, 19.7% 15 mg *vs* 1.3% placebo at 3.4 years[24]
% patients achieving >5% weight loss			In obesity 63.2% *vs* 27.1% placebo[14] In T2D 54.3% *vs* 21.4% placebo[25]	In T2D 54%[15]	In obesity 86.4% *vs* 31.5% placebo[16] In T2D 68.8% *vs* 28.5% placebo[17]	In obesity 85% 5 mg, 89% 10 mg, 91% 15 mg *vs* placebo 35%[18] In T2D 65% 5 mg, 76% 10 mg, 80% 15 mg[15]
% patients achieving >10% weight loss			In obesity 33.1% *vs* 10.6% placebo[14] In T2D 25.2% *vs* 6.7% placebo[25]	In T2D 24%[15]	In obesity 69.1% *vs* 12.0% placebo[16] In T2D 45.6% *vs* 8.2% placebo[17]	In obesity 69% 5 mg, 78% 10mg, 84% 15 mg *vs* 19% placebo[18] In T2D 34% 5 mg, 47% 10 mg, 57% 15 mg[15]
% patients achieving >15% weight loss			In obesity 14.4% *vs* 3.5% placebo[14] In T2D not reported	In T2D 8%[15]	In obesity 50.5% *vs* 4.9% placebo[16] In T2D 25.8% *vs* 3.2% placebo[17]	In obesity 30% 5 mg, 50% 10 mg, 57% 15 mg *vs* 3% placebo[18] In T2D 15% 5 mg, 24% 10 mg, 36% 15 mg[15]
Dose and cost of medication per month†	1.5 mg weekly $135 PBS $31.50	1.2 to 1.8 mg daily $170 to $255	3 mg daily $387	1 mg weekly $140 PBS $40	0.25 to 1 mg weekly $260, 1.7 to 2.4 mg weekly $380	2.5 weekly $285 5 mg weekly $395, 7.5 to 10 mg weekly $545, 12.5 to 15 mg weekly $695‡

Abbreviations: T2D = type 2 diabetes.
* Semaglutide 1 mg (Ozempic) is TGA approved for type 2 diabetes; semaglutide 2.4 mg (Wegovy) is TGA approved for chronic weight management and to reduce the risk of major adverse CV events in people with established CV disease and a BMI of ≥27 kg/m^2 without established type 1 or type 2 diabetes; tirzepatide (Mounjaro) is TGA approved for type 2 diabetes, chronic weight management and obstructive sleep apnoea in patients with obesity.
† Estimated price from pharmacy websites for private prescription.
‡ Prices listed as of July 2025.

taking semaglutide 2.4 mg weekly for weight loss regained two-thirds of their prior weight loss within a year of stopping the medication.[31] This is unsurprising as, like nearly all medications, these agents are effective only while in use and lose efficacy once ceased. Whether weight loss can be maintained with lower doses after patients have sustained a stable reduced weight for several years remains to be determined.

Benefits beyond weight loss

Liraglutide, semaglutide (2.4 mg weekly dose) and tirzepatide lower blood pressure, improve lipid profiles, reduce blood glucose levels, reduce C-reactive protein levels and improve physical functioning.[14,16,18] These effects appear associated with both weight loss and weight-independent effects of GLP-1 receptor agonists.[32] Given these substantial beneficial effects on cardiometabolic risk factors, it is unsurprising that incretins have also been shown to reduce the risk of cardiometabolic diseases.

Prevention of type 2 diabetes

In adults with prediabetes and obesity, liraglutide 3 mg daily for three years reduced the risk of progression to type 2 diabetes by 79%, with a greater proportion reverting to normoglycaemia.[20] Similarly, semaglutide 2.4 mg once weekly for one year in adults with prediabetes and obesity resulted in reversion to normoglycaemia in 81% compared with 14% on placebo.[33] Even more impressively, three years of tirzepatide treatment reduced the risk of progression to type 2 diabetes by 93% among adults with prediabetes versus placebo ($p < 0.0001$).[24]

Cardiovascular effects

Incretin analogues increase heart rate by about two to three beats per minute via indirect stimulation of sinoatrial nodal tissue through increased sympathetic nervous system activation. Although this could potentially have adverse cardiac effects, GLP-1 receptor agonists have been shown to protect cardiac myocytes against ischaemia in animal and human studies. Interestingly, GLP-1 receptor agonists oppose sympathetic effects on cardiac ventricular excitability, reducing ventricular arrhythmic risk through stimulation of cardiac parasympathetic neurons. This, along with their beneficial effect on lipid levels, inflammation and glucose uptake, likely contributes to their beneficial cardiac effects.[32,34]

After a median exposure of 3.8 years to liraglutide 1.8 mg daily in patients with type 2 diabetes, the primary composite outcome – death from cardiovascular causes, nonfatal myocardial infarction and nonfatal stroke – was reduced by 13%, with death from cardiovascular causes reduced by 22%.[35]

In people with type 2 diabetes and established cardiovascular disease, two years of low-dose semaglutide (0.5 or 1 mg) reduced the risk of a composite outcome of cardiovascular death, nonfatal myocardial infarction or nonfatal stroke by 26%, primarily driven by stroke reduction.[36] In people without diabetes but with obesity and pre-existing cardiovascular disease, semaglutide 2.4 mg once weekly reduced the risk of death from cardiovascular causes, nonfatal myocardial infarction or nonfatal stroke by 20% over a median of 3.25 years.[22] Semaglutide 2.4 mg once weekly has also been shown to result in greater improvements in exercise function and greater reduction in symptoms associated with heart failure in people with heart failure with preserved ejection fraction.[37]

In people with obesity and heart failure with preserved ejection fraction, one year of tirzepatide treatment lowered the risk of a composite of death from cardiovascular causes or worsening heart failure by 38%.[38] A substudy of this trial showed tirzepatide reduced left ventricular mass and paracardiac adipose tissue.[39] Cardiovascular outcome trials with tirzepatide are underway but real-world data suggest it may provide better cardiovascular outcomes in people aged over 40 with type 2 diabetes and established cardiovascular disease compared with GLP-1 receptor agonists.[40]

A recent trial showed that semaglutide 1 mg once weekly increased maximum walking distance by 13% in people with type 2 diabetes and peripheral vascular disease.[41]

Renal effects

In people with type 2 diabetes at high risk of cardiovascular disease, liraglutide 1.8 mg daily over a median follow up of 3.8 years resulted in a 22% reduction in renal outcomes compared with placebo. This result was driven mainly by a lower incidence of macroalbuminuria in the liraglutide group than in the placebo group.[42] Similarly, semaglutide (0.5 or 1 mg once weekly) over two years in people with type 2 diabetes resulted in a 36% reduction in the progression of nephropathy compared with placebo.[36] However, these studies were not primarily designed to assess renal outcomes and the benefits seen were mainly attributable to reductions in albuminuria. The Evaluate Renal Function with Semaglutide Once Weekly (FLOW) study was designed to assess the effect of semaglutide 1 mg once weekly on kidney outcomes in patients with chronic kidney disease and type 2 diabetes. The trial was stopped early based on a prespecified interim analysis, with a median follow up of 3.4 years. Semaglutide treatment resulted in a 24% reduction in major kidney disease, a composite of kidney failure, at least a 50% reduction in estimated glomerular filtration rate from baseline or death from kidney-associated or cardiovascular causes.[43]

Clinical trials of tirzepatide in people with renal disease are still ongoing. However, early evidence suggests potential renal benefits. In a post hoc analysis using pooled data from five trials (SURPASS-1 to -5) in people with type 2 diabetes and urinary albumin-to-creatinine ratio of 3.4 mg/mmol and above, tirzepatide was associated with a 19 to 26% reduction (depending on dose used) in urinary

albumin-to-creatinine ratio compared with placebo or insulin. However, after 40 to 42 weeks, no significant difference in estimated glomerular filtration rate was observed.[44] A retrospective cohort study of people with type 2 diabetes aged 18 years and older found that tirzepatide was associated with lower rates of all-cause mortality, cardiovascular events, acute kidney injury and adverse kidney events compared with GLP-1 receptor agonists.[45]

Liver disease

In a 72-week phase 2 study of patients (n = 320) with metabolic dysfunction-associated steatohepatitis (MASH), semaglutide (0.1, 0.2 or 0.4 mg daily) reduced steatosis but had no effect on fibrosis.[46] In an open-label substudy of patients with type 2 diabetes and MASH (n = 502), tirzepatide resulted in a significant reduction in liver fat compared with insulin degludec after 52 weeks.[47] In a smaller 48-week trial (n = 71) of semaglutide 2.4 mg once weekly in people with biopsy-confirmed MASH and compensated cirrhosis, there was no significant improvement in fibrosis or resolution of MASH compared with placebo.[48] However, an interim analysis at 72 weeks of a phase 3 trial of semaglutide 2.4 mg once weekly for MASH showed histological improvements, including resolution of fibrosis, reduction of liver fibrosis and resolution of steatohepatitis in a significant number of patients.[49]

Tirzepatide also shows promise. In a phase 2 trial of people with biopsy-confirmed MASH, tirzepatide treatment over 52 weeks led to resolution of MASH in 34 to 53% of participants (depending on the dose used) compared with placebo. There was also an indication of improved fibrosis without worsening of MASH with tirzepatide.[50]

Obstructive sleep apnoea

In a one-year study of adults with moderate to severe obstructive sleep apnoea and obesity – about half of whom were treated with positive airway pressure at baseline – tirzepatide 10 or 15 mg once weekly resulted in a clinically meaningful reduction in the apnoea–hypopnoea index compared with placebo. Tirzepatide also significantly reduced the sleep apnoea-specific hypoxic burden, a measure that comprises the frequency, duration and depth of oxygen desaturation associated with sleep events, and is considered a better predictor of cardiovascular risk and mortality in sleep apnoea. Treatment was also associated with reductions in body weight, high-sensitivity C-reactive protein level, systolic blood pressure and improvements in sleep-associated patient-reported outcomes.[51]

Neurodegenerative disease

Animal studies suggest that GLP-1 analogues exert a range of beneficial effects on cognitive function in models of Alzheimer's disease. These include improvements in learning and memory, reductions in amyloid plaques and tau phosphorylation, attenuation of cortical and hippocampal neuronal loss, increased neurogenesis, improved synapsis number and plasticity, reduced brain oxidative stress, cerebral anti-inflammatory activity and improved brain insulin receptor localisation and signalling.[52,53] GLP-1 receptor agonists have also shown benefit in animal models of Parkinson's disease, with greater effects observed using GLP-1/GIP dual receptor agonists.[52]

Although dementia was not a primary outcome, a pooled analysis of 15,820 patients with type 2 diabetes randomised to GLP-1 receptor agonist treatment or placebo found a 50% reduction in dementia progression over a median of 3.6 years (15 cases in the placebo group *vs* 32 in the GLP-1 receptor agonist group).[53] A nationwide cohort study of 120,054 patients with type 2 diabetes over a median follow up of 7.4 years found an 11% reduction in the rate of dementia with GLP-1 receptor agonists (95% of patients were on liraglutide) when used as a second-line treatment compared with other glucose-lowering therapies, with greater benefit seen with longer duration of use.[53] However, these studies were observational or post hoc analyses, and dementia was not the primary outcome.[52,53]

Two recent trials further support a possible role for GLP-1 analogues in dementia prevention. An analysis of electronic health records from over one million people with type 2 diabetes and no prior diagnosis of dementia found that semaglutide use was associated with a 40 to 70% reduced risk developing dementia over three years, depending on the comparator medication, with the greatest benefit seen when compared to insulin.[54] A systemic review and meta-analysis of randomised clinical trials evaluating cardioprotective glucose-lowering medications also found that GLP-1 receptor agonists were associated with a significant reduction in dementia risk.[55] While promising, these findings are not definitive due to the lack of randomised clinical trials with dementia as the primary outcome, and further evidence is required. Two phase 3 trials are currently underway investigating once-daily oral semaglutide in early-stage Alzheimer's disease (clinical trial numbers NCT04777396 and NCT04777409).

Small clinical trials of exenatide and liraglutide in people with Parkinson's disease have shown improvements in motor symptoms, emotional wellbeing, activities of daily living and quality of life.[52] However, in a 96-week phase 3 trial (n=194) of once-weekly exenatide 2 mg in people with moderately severe Parkinson's disease (without diabetes), there was no significant improvement in Parkinson's disease severity compared with placebo.[56]

Adverse effects

Gastrointestinal effects

The most common adverse events associated with GLP-1 receptor agonist treatment are gastrointestinal, particularly nausea, followed by diarrhoea, vomiting and constipation. These symptoms usually subside over time, and slow dose titration can minimise their occurrence. Nonetheless, gastrointestinal side effects led to treatment

discontinuation in 4.5% of participants in semaglutide trials and 6.2% of those receiving the highest dose (15 mg weekly) of tirzepatide.[16,18]

Early concerns about pancreatic safety arose from reports of pancreatitis in animal studies with the use of sitagliptin, clinical reports of humans treated with exenatide and the detection of preneoplastic pancreatic ductal lesions in animals treated with GLP-1 receptor agonists. Use of these agents has been associated with a modest increase in lipase and amylase levels (by 15 and 37%, respectively, in one study[46]), but this is rarely of any clinical significance. A comprehensive review of preclinical toxicology in animals with and without diabetes by European and US regulatory authorities found no evidence of incretin-associated pancreatic toxicity. There has been no evidence of increased pancreatic disease in the large cardiovascular outcome trials studying the safety of GLP-1 receptor agonists.[57]

However, in a Canadian study using data from a large health claims database, comparing the use of a GLP-1 receptor agonist with naltrexone/bupropion to treat obesity, there was an increased risk of pancreatitis. Although the event rate was low (4.6/1000 person-years for semaglutide, 7.9 for liraglutide and 1.0 for bupropion/naltrexone), there was a ninefold increased risk with GLP-1 receptor agonists overall.[58]

Some studies have reported an increased risk of biliary disease, including cholelithiasis and acute cholecystitis, with the use of GLP-1 receptor agonists. However, animal studies do not support these agents having a direct effect on the biliary system. As weight loss increases the lithogenicity of bile, it remains unclear whether the increased risk of biliary disease seen with GLP-1 receptor agonists is due to the medication itself or to weight loss.[57]

Anaesthesia

Several studies, including a retrospective audit and a matched pair case-control study of 205 pairs of patients undergoing gastroscopy, have shown that patients taking GLP-1 receptor agonists have higher rates of retained solid gastric contents.[59] There have also been case reports of pulmonary aspiration when under anaesthesia in patients taking GLP-1 receptor agonists.[59] Given the long half-life of these agents, stopping them before surgery is of limited value, and is not feasible in emergency procedures.

The American Society of Anesthesiologists recommends managing patients on GLP-1 receptor agonists as if they have a full stomach, including appropriate airway protection and rapid sequence induction.[57] Similar recommendations have been made by Australian experts. Additionally, it has been recommended that patients having elective procedures consume only clear fluids for 24 hours before surgery. Australian guidelines also provide detailed advice on patient preparation before elective upper endoscopy.[60]

Medullary thyroid cancer

There is a theoretical increased risk of medullary thyroid cancer (MTC) as preclinical studies showed a link between GLP-1 receptor agonism to the development of C-cell hyperplasia and MTC in rodents. Although GLP-1 receptors are expressed in rodents and have a functional role in bone metabolism, the density of GLP-1 receptors in monkey and human thyroid cells is extremely low. Clinical trials have shown no evidence of increased calcitonin levels (which have been measured in all clinical trials of GLP-1 receptor agonists) or MTC rates with GLP-1 receptor agonist use. Nevertheless, as some human MTCs may express GLP-1 receptors, these agents are not recommended for individuals with a personal or family history of MTC or multiple endocrine neoplasia type 2.[57]

Ophthalmic complications

After two years of low-dose semaglutide 1 mg once weekly in people with type 2 diabetes, there was a 76% increased risk of worsening retinopathy compared with placebo, although the absolute event rate was low (3.0% with semaglutide *vs* 1.8% with placebo).[36] Similarly, in a retrospective cohort study of 3435 people with type 2 diabetes exposed to tirzepatide for 180 days and over compared with a matched unexposed cohort, tirzepatide was associated with an increased risk of new-onset proliferative diabetic retinopathy – primarily in those with pre-existing nonproliferative diabetic retinopathy. There were very few cases in participants with no or very mild retinopathy at baseline, and no progression of mild nonproliferative diabetic retinopathy was observed.[61] GLP-1 receptors are not present in ocular tissue, so it is likely that any worsening of retinopathy is associated with the rapid glucose lowering observed with these agents.[3]

Nonarteritic anterior ischaemic optic neuropathy (NAION), the second most common form of optic neuropathy and a leading cause of adult blindness, has also emerged as a potential concern. A retrospective matched cohort study found a significantly higher risk of NAION among people with diabetes and those with overweight or obesity taking semaglutide compared with those not on GLP-1 receptor agonist treatment.[62] A case series linked the use of semaglutide or tirzepatide with an increased risk of NAION, sometimes after a single dose, including in one patient without diabetes and in another who experienced symptoms in both eyes following separate doses. Rapid correction of glycaemia with resultant optic nerve swelling has been hypothesised as a factor. Other reported complications included bilateral papillitis and paracentral acute middle maculopathy, both in people with type 2 diabetes. These findings suggest a higher risk of acute ocular complications in people with type 2 diabetes.[63] However, several studies have found no association between synthetic incretins and NAION, and a recent review concluded that no definitive causal relationship has been established between these agents and NAION.[64]

Psychiatric disease

A bidirectional relationship exists between obesity and depression, with each increasing the risk of the other.[65] Given this, it is not unexpected that case reports of suicide in people taking incretin treatment have been documented, and these are being monitored by the European Medicines Agency and the US Food and Drug Administration. However, a retrospective cohort study of electronic health records involving 240,618 patients with overweight or obesity prescribed semaglutide or non-GLP-1 receptor agonist antiobesity medications, and 1,589,855 patients with type 2 diabetes prescribed semaglutide or other hypoglycaemic agents, found a lower risk of suicidal ideation in patients prescribed semaglutide regardless of prior psychiatric history.[66] Although people with significant psychiatric illness are typically excluded from clinical trials, no increase in psychiatric disorders has been observed in these studies. In contrast, improvements in quality of life measures have been reported with incretin therapy.

The future of incretins and new agents

Incretin analogues have proven to be very popular, with global shortages precipitated by high demand, which has been particularly problematic for patients. These medications must only be used by people with health problems and not by healthy individuals with minimal or no excess adiposity who are seeking weight loss for purely cosmetic reasons. However, as the production of approved medications increases, and with the arrival of new products currently undergoing phase 2 and 3 studies, availability is expected to improve. Products in more advanced studies include a combination of cagrilintide (an amylin analogue) and semaglutide; retatrutide, a triple compound of GIP, GLP-1 and glucagon receptor agonists; survodutide, a dual glucagon and GLP-1 receptor agonist; maridebart and cafraglutide, a dual GIP receptor antagonist and GLP-1 receptor agonist; and orforglipron, an oral nonpeptide GLP-1 receptor agonist.[67]

Conclusion

Incretin analogues are very effective weight loss medications with cardiovascular, renal, respiratory and hepatic benefits, with emerging evidence suggesting potential neuroprotective effects. Adverse effects are generally limited to gastrointestinal disturbances, which can be managed through dose reduction and caution around anaesthesia. Liraglutide, semaglutide and tirzepatide have been shown to reduce major cardiovascular events, and similar trials are ongoing for other investigational incretins. Currently, no medications for overweight and obesity are subsidised by the PBS, which is a significant concern given that obesity disproportionately affects people of lower socioeconomic status. The Pharmaceutical Benefits Advisory Committee will need to weigh the broad availability of incretin analogues for obesity management against the long-term health and economic costs of obesity to the Australian community. MT

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A list of references is included in the online version of this article (https://medicinetoday.com.au/mt/2025/august/supplements/focus-obesity-collection).

COMPETING INTERESTS: Associate Professor Markovic is an investigator on pharmaceutical trials of semaglutide and CagriSema (NovoNordisk), tirzepatide and retatrutide (Lilly), BI 456906 (Boehringer Ingelheim) and maridebart/cafraglutide (Amgen); and is on the Advisory Board for Nestlé Health Science, VLCD. Associate Professor Hocking has received honoraria for lectures and manuscript writing from Lilly Australia, AstraZeneca, Amgen, Sanofi-Aventis, Nestlé Health Sciences, iNova and Servier; support for attending meetings from Lilly Australia, Novo Nordisk, Amgen and CSL Seqirus; participation on Advisory Boards from Lilly Australia, Novo Nordisk, Ethicon and AstraZeneca; is an investigator on pharmaceutical trials of semaglutide and CagriSema (NovoNordisk), tirzepatide and retatrutide (Lilly), BI 456906 (Boehringer Ingelheim) and maridebart/cafraglutide (Amgen); and is President of the National Association of Clinical Obesity Services.

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New pharmacological treatments for obesity

Incretin analogues, their mechanism of action, efficacy and safety

TANIA P. MARKOVIC MB BS, PhD, FRACP
SAMANTHA L. HOCKING MB BS, MMed(Clin Epi), FRACP, PhD

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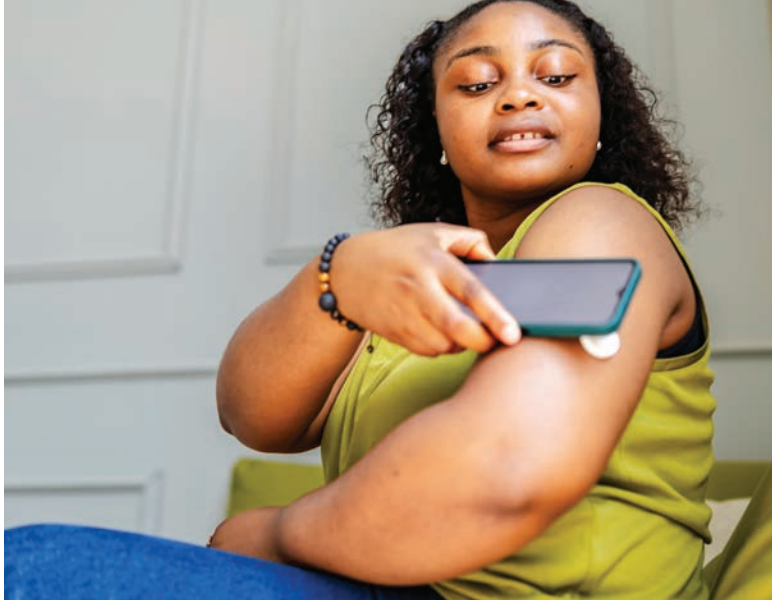
Concurrent management of type 2 diabetes and obesity



TESSA WEIR MB BS, FRACP
SARAH GLASTRAS BSc(Hons), MB BS(Hons), FRACP, PhD

Type 2 diabetes is prevalent in Australia, with most diagnosed patients also being affected by comorbid obesity. Weight loss can mitigate otherwise substantial risk in people with obesity and diabetes. Strategies for the management of weight in patients with type 2 diabetes include lifestyle modifications, pharmacotherapy and surgery.

Key points

- **The prevalence of both diabetes and obesity is rapidly increasing in Australia.**
- **Weight loss improves the core metabolic features common to both conditions and reduces morbidity and mortality.**
- **Lifestyle interventions and pharmacotherapy should be introduced early.**
- **Glucagon-like peptide-1 receptor agonists and dual incretin agonists are among the most effective medications to manage type 2 diabetes and obesity concurrently.**
- **Surgical intervention is a treatment option for the minority of people with type 2 diabetes and obesity.**

Diabetes occurs in 5.3% of people in Australia, with 1.3 million people living with the condition in 2022, the majority of whom have type 2 diabetes (T2DM).[1] Diabetes contributed to 11% of all deaths in 2022.[2] Obesity is one of the leading risk factors for developing T2DM, and almost 80 to 90% of people with T2DM have overweight or obesity.[3] Obesity has become an increasing problem worldwide, with 66% of adults in Australia having a body mass index (BMI) in either the overweight (25 to 29.9 kg/m^2) or obesity (≥30 kg/m^2) range.[4] As the prevalence of obesity increases, there is also a rise in obesity-associated complications, leading to further morbidity and mortality. These complications include hypertension, hyperglycaemia, cardiovascular (CV) disease, T2DM, dyslipidaemia, airway disease, obstructive sleep apnoea, metabolic dysfunction-associated steatohepatitis (MASH), gastro-oesophageal reflux disease, urinary stress incontinence and osteoarthritis.[5-7]

Compared with people who have a BMI within a healthy range, those with obesity have a significantly increased risk of obesity-associated comorbidities. Women have a 12.4-fold increased risk of developing T2DM, almost double the risk seen in men.[8] In the context of obesity, women also have a higher risk of developing coronary artery disease, which is especially concerning given CV disease is the leading cause of death in both men and women.[6] The rate of other complications is just as alarming, with more than one in 20 cancer cases directly associated with with overweight or obesity.[7] Obesity is the second most common modifiable risk factor (after smoking) for developing cancer. Therefore, maintaining a healthy weight could be crucial for the primary prevention of a large disease burden in the future (Flowchart).

Benefits of weight loss

Weight loss can mitigate otherwise substantial risk in people with obesity and T2DM, with even modest reductions in weight (<5%) leading to improvements in hypertension and hyperglycaemia.[9] A 5 to 10% weight loss is associated with a reduction of intrahepatic lipids in metabolic-associated fatty liver disease; improvement in forced expiratory volume at one second in those with asthma and airway disease; reduction in triglyceride levels, increase in high-density lipoprotein cholesterol and reduction in nonhigh-density lipoprotein cholesterol; improvements in ovulation and regularisation of menses, particularly in women with polycystic ovary syndrome; and prevention of T2DM.[9,10] A 10% weight loss also results in a reduction in all-cause mortality.[11] More progressive weight loss (>10%) significantly improves metrics associated with osteoarthritis (including pain, walking distance and quality of life scores), gastro-oesophageal reflux disease, obstructive sleep apnoea, nonalcoholic steatohepatitis and heart failure with preserved ejection fraction (HFpEF).

Furthermore, achieving greater than 10% weight loss is associated with reductions in CV disease mortality and increased rates of T2DM

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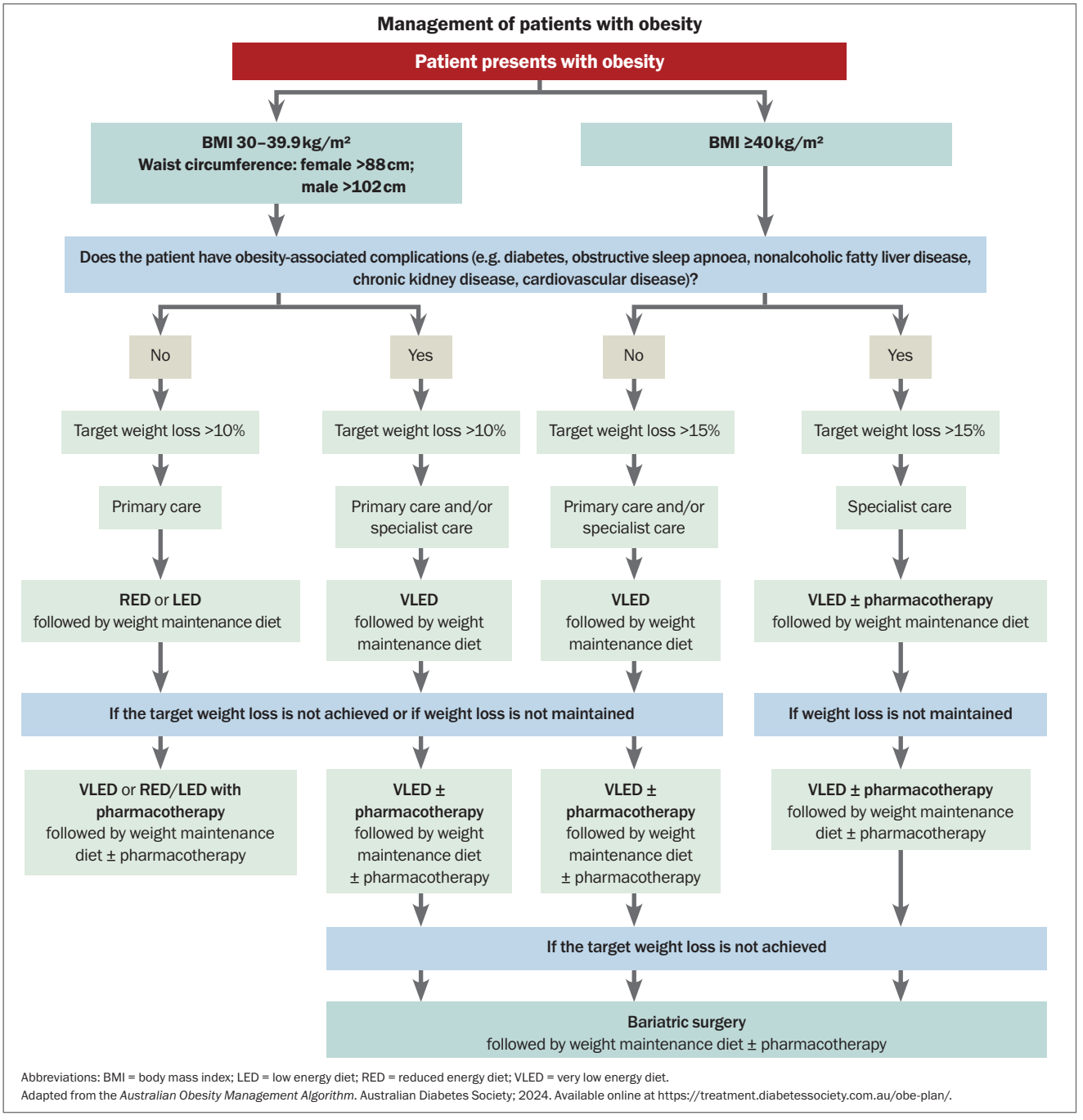
Dr Weir is a Staff Specialist at Nepean Hospital, Sydney; and a Consultant Endocrinologist at Specialists on Derby, Sydney. Associate Professor Glastras is Head of Department, and a Senior Staff Specialist at the Royal North Shore Hospital, Sydney; and a Consultant Endocrinologist at the Northern Sydney Endocrine Centre, Sydney, NSW.



Abbreviations: BMI = body mass index; LED = low energy diet; RED = reduced energy diet; VLED = very low energy diet.
Adapted from the *Australian Obesity Management Algorithm*. Australian Diabetes Society; 2024. Available online at https://treatment.diabetessociety.com.au/obe-plan/.

remission, especially when the duration of T2DM is short (Box).[9-13]

Therapeutic strategies for diabetes and obesity management

Lifestyle intervention

The Diabetes Remission Clinical Trial (DiRECT) demonstrated that lifestyle intervention implemented in general practice for people with T2DM can lead to meaningful weight loss and disease remission.[9] After an initial three-month period of a reduced energy diet (about 850 kcal/day) and a further six-week food reintroduction phase, participants were randomised to receive either standard care or a structured program providing individualised dietary advice and an exercise program. At one year, 46% of participants in the intervention arm were in remission (defined as a glycated haemoglobin [HbA_{1c}] <6.5% without medications) and 24% had achieved the target weight loss of 15 kg or more. Although the number of participants who maintained sustained weight loss reduced over the following year, there was still evidence of a benefit, with 36% of those in the intervention arm remaining in T2DM remission. This pivotal trial provides evidence that, beyond weight reduction, lifestyle intervention can facilitate remission of T2DM.

Physical activity should always be encouraged in conjunction with dietary interventions, with key objectives tailored to individuals

and available resources. Standard recommendations include 150 minutes of moderate-to-vigorous intensity exercise per week. However, exercise physiologists advise against rigid prescriptions of physical activity or setting unachievable goals, and instead recommend focusing on activities the patient enjoys, such as dancing, yoga or swimming. There is strong evidence linking physical inactivity with an increased risk of many adverse health conditions. Globally, physical inactivity is associated with 9% of premature mortality, meaning over five million deaths per year could be prevented.[14] In people with obesity and T2DM, studies of physical activity interventions have shown that early intervention can prevent or ameliorate weight gain and its health consequences, while also improving insulin sensitivity and lowering blood glucose levels (Table 1).[15] For those on insulin, basal requirements can reduce as much as 30% after high-intensity interval exercise. As such, close glucose monitoring is required to make appropriate treatment adjustments when physical activity is planned.[16]

Although lifestyle interventions have demonstrated benefits in morbidity and mortality, the LookAHEAD trial highlights the complexity of relationships among weight loss, glycaemic control and CV outcomes for individuals with T2DM.[17] Despite achieving significant and sustained weight loss through caloric restriction and increased physical activity over an almost 10-year period, trial participants did not have a statistically significant reduction in CV events. However, the intervention did lead to improved glycaemic control, blood pressure and lipid levels, as well as a higher rate of achieving and maintaining clinically significant weight loss. Some of these findings may be attributable to the unblinded nature of the study and potential selection bias favouring the inclusion of more health-conscious patients. Regardless, these findings underscore the intricate interplay of factors influencing CV outcomes within the context of lifestyle interventions for people with T2DM.

Very low energy diets

Although the sustained rate of T2DM remission in DiRECT was reassuring, there was a trend towards weight regain during the follow-up period. An analysis of eight high-quality weight loss studies showed that, without continued intervention, weight regain occurred in most people.[18] Strategies that are easy to implement and support ongoing low caloric intake help reduce weight regain. Very low energy diets (VLEDs) are useful in this context by providing 800 calories per day while ensuring the patient still has adequate intake of essential vitamins, minerals and amino acids. The low carbohydrate content of VLEDs induces a mild ketosis after two to three days.

Despite their efficacy, the practical implementation of VLEDs necessitates careful consideration of individual circumstances and challenges; a substantial proportion of patients face difficulties in adhering to and managing VLEDs. Reduced energy diets and low energy diets are available as milder alternatives to VLEDs. Certain patients may be unsuitable for VLEDs, including those at risk of malnutrition or ketoacidosis (e.g. individuals prescribed a sodium-glucose cotransporter-2 [SGLT-2] inhibitor), individuals with a history of eating disorders and pregnant or lactating women. Patients on VLEDs may experience fluctuations in glucose levels, requiring careful monitoring and potential adjustments to medication.

Despite these considerations, the benefits of the appetite-suppressing effects of VLEDs make them a noteworthy consideration in managing T2DM and obesity. VLEDs should be considered as an initial weight loss strategy if supervised lifestyle interventions have been unsuccessful in reducing weight, or if rapid weight loss is required (e.g. prior to bariatric or general surgery conditional on weight loss). Physical activity should be encouraged alongside VLEDs, which can be safely used in conjunction with other weight loss strategies. Intermittent use may also assist with long-term weight management.

Pharmacotherapy

Although the above lifestyle strategies can help to lower body weight and induce T2DM remission, maintaining long-term weight loss with lifestyle intervention alone is difficult.[19] Pharmacotherapy can assist patients with weight loss and maintenance. A significant barrier to ongoing pharmacotherapy use in Australia is cost, as the long-term use of weight loss medications remains expensive and often prohibitive for many people. Unfortunately, obesity management is strongly dictated by affordability.

In Australia, six antiobesity medications are currently TGA approved for patients with obesity, or overweight with medical comorbidities: orlistat, phentermine, combination naltrexone/bupropion, liraglutide, semaglutide (2.4 mg weekly dose) and tirzepatide (Table 2).

Orlistat

Orlistat induces weight loss by inhibiting gastric and pancreatic lipases, thereby preventing the hydrolysis of triglycerides and reducing the absorption of free fatty acids. Apart from its beneficial effects on weight, no direct glucose-lowering effects have been recognised with the use of orlistat.

Phentermine

Phentermine is an adrenergic agonist that increases noradrenaline release in the lateral hypothalamus. It is thought to promote weight loss through the inhibition of neuropeptide Y, a key mediator in hunger perception, although its precise mechanism remains unclear. As with orlistat, phentermine does not exhibit direct glucose-lowering effects.

Conditions improved by weight loss[9-13]

0–5% weight loss
- Hypertension
- Hyperglycaemia

5–10% weight loss
- Type 2 diabetes
- Polycystic ovarian syndrome
- Dyslipidaemia
- Asthma and airway disease
- Nonalcoholic fatty liver disease

10–15% weight loss
- Cardiovascular disease
- Urinary stress incontinence
- Nonalcoholic steatohepatitis
- Obstructive sleep apnoea syndrome
- Gastro-oesophageal reflux disease
- Knee osteoarthritis

>15% weight loss
- Type 2 diabetes remission
- Cardiovascular mortality
- Heart failure with preserved ejection fraction

Table 1. Effect of exercise modalities on health outcomes in type 2 diabetes[14]

Health outcome	Exercise modality			
	Aerobic exercise	Resistance exercise	Flexibility exercise	Balance exercise
Glycaemic control	+++	++	–	–
Cardiovascular risk reduction	+++	+	–	–
Mental health	+++	+	–	–
Balance	+	+	++	+++
Muscle strength	+	+++	–	+
Bone health	+	+++	–	–

Key: +++ = strong benefit; ++ = moderate benefit; + = minor benefit; – = no benefit.
Reproduced with permission from The Royal Australian College of General Practitioners from: Williams A, Radford J, O'Brien J, Davison K. Aust J Gen Pract 2020; 49: 189-193.[14]

Naltrexone/bupropion

Although the exact neurochemical effects of naltrexone/bupropion are not fully understood, bupropion directly increases pro-opiomelanocortin activity, and naltrexone indirectly increases pro-opiomelanocortin activity by blocking its natural negative feedback loop.[20] In mouse models, direct administration into the brain reduces food intake by altering the mesolimbic reward circuit and increases the firing rate of pro-opiomelanocortin neurons that regulate appetite. In people with established T2DM, a 12-month trial of naltrexone/bupropion demonstrated a reduction in HbA_{1c} of 0.6% in participants who achieved a 5% body weight loss in the first 16 weeks, with a 9% body weight loss at 12 months.[21]

Liraglutide and semaglutide

The Australian Diabetes Society, Australian and New Zealand Obesity Society and Royal Australian College of General Practitioners recommend the early use of glucagon-like peptide-1 receptor agonists (GLP-1RAs), such as liraglutide and semaglutide, for the management of T2DM and obesity.[22,23] The primary mechanism of action of GLP-1RAs involves activation of the incretin pathway, which acts on the central nervous system to reduce appetite, leading to reduced food intake and subsequent weight loss.[24] Incretin-based therapy with GLP-1RAs also stimulates insulin release from pancreatic beta cells, resulting in reductions in both body weight and blood glucose levels in people with T2DM.[25] In patients with obesity, a 56-week treatment with liraglutide 3 mg led to a cumulative reduction in the risk of developing T2DM, as well as a mean body weight loss of 8.4 kg.[26] In people with established prediabetes and obesity, three years of liraglutide treatment led to a threefold increase in the likelihood of normoglycaemia.[27] After a 30-week treatment course, liraglutide reduced HbA_{1c} by 1.55% and led to a mean body weight loss of 4.53 kg.[28]

Semaglutide 1.0 mg, administered once weekly by subcutaneous injection, has been shown to lower body weight and sustain body weight reduction over a two-year trial period, with up to two-thirds of patients achieving a clinically meaningful reduction of at least 5% of their initial body weight.[28] In addition to weight loss, semaglutide 1.0 mg has demonstrated significant glucose-lowering potential. Head-to-head trials have shown it to be superior to dipeptidyl peptidase-4 inhibitors, SGLT-2 inhibitors and other GLP-1RAs, with a mean HbA_{1c} reduction of 1.5 to 1.8%, and 80% of patients achieving an HbA_{1c} of less than 7%.[29-32] Several studies on GLP-1RAs have also demonstrated CV benefits, with up to a 26% reduction in CV risk in high-risk patients.[28,33-35] The FLOW trial showed a 24% reduction in the risk of major kidney disease events, an 18% reduction in cardiovascular events, and a 20% reduction in all-cause mortality among participants with T2DM and chronic kidney disease (CKD) treated with semaglutide compared to placebo.[36]

Semaglutide has also shown promise in treating MASH. In the ESSENCE trial involving participants with biopsy-confirmed MASH and stage 2 or 3 fibrosis, over half of whom had T2DM, interim analysis at 72 weeks showed 63% of those treated with semaglutide 2.4 mg weekly achieved resolution of steatohepatitis without worsening of fibrosis, compared with 34% in the placebo group.[37]

Semaglutide 2.4 mg reduces body weight by 16% in people with obesity, or with overweight (BMI ≥27 kg/m^2) and a medical comorbidity.[38] The pivotal SELECT trial demonstrated, for the first time, that a weight loss medication could provide CV benefit – specifically, semaglutide 2.4 mg significantly reduced major adverse CV events by 20% in people with obesity and established CV disease, without diabetes, over a median follow up of 3.3 years.[39] Semaglutide (2.4 mg weekly dose) is also TGA approved to reduce the risk of major adverse CV events in people with established CV disease and a BMI of ≥27 kg/m^2 without established type 1 or type 2 diabetes. In this population, semaglutide 2.4 mg significantly reduced heart failure symptoms and body weight, while improving physical function, as evidenced by increased six-minute walk test distance.[40]

Semaglutide is approved for weight management in a 2.4 mg weekly dose formulation, which has TGA approval but is not listed on the PBS. The 1.0 mg weekly dose of semaglutide, indicated for T2DM, has PBS listing under restricted criteria. Specifically, it must be prescribed in combination with at least one of metformin, a sulfonylurea or insulin, and only when glycaemic control remains inadequate despite treatment (with at least one of metformin, a sulfonylurea or insulin). Furthermore, semaglutide (1 mg weekly dose) cannot be coprescribed on the PBS alongside an SGLT-2 inhibitor, dipeptidyl peptidase-4 inhibitor or another GLP-1RA. Due to ongoing supply constraints, regulatory authorities advise that the 1.0 mg formulation should not be prescribed solely for weight loss. To ensure appropriate and equitable access, the 2.4 mg formulation should be prescribed in patients in whom semaglutide is indicated for weight management.

Table 2. Properties of medications with TGA approval for chronic weight management*

Drug properties	Phentermine (Duromine, Metermine, Phentermine Juno)	Orlistat (Xenical)	Naltrexone/ bupropion (Contrave)	Liraglutide (Saxenda)	Semaglutide (Wegovy)†	Tirzepatide (Mounjaro)†
Formulation	Tablet	Tablet	Tablet	Solution for subcutaneous injection in a prefilled pen	Solution for subcutaneous injection in a prefilled pen	Solution for subcutaneous injection in a prefilled pen
Starting dose	15 mg in the morning	120 mg three times a day	8 mg/90 mg daily	0.6 mg once daily	0.25 mg once weekly	2.5 mg once weekly
Dose escalations and maintenance doses	• Maintenance dose: 15 mg to 40 mg daily (continuous or intermittent)	• N/A	• Increase by one tablet weekly	• Increase dose by 0.6 mg daily per week • Maintenance dose: 3.0 mg	• Increase to 0.5 mg in weeks 5–8, 1 mg in weeks 9–12 and 1.7 mg in weeks 13–16 • Maintenance dose: 2.4 mg	• Increase by 2.5 mg every four weeks • Maintenance doses: 5 mg, 10 mg
Maximum dose	40 mg daily	120 mg three times a day	16 mg/180 mg twice a day	3 mg once daily	2.4 mg once weekly	15 mg once weekly
Adverse effects	• Hypertension • Tachycardia • Insomnia • Restlessness • Dry mouth • Diarrhoea • Constipation	• Steatorrhoea • Fat-soluble vitamin deficiency	• Nausea • Vomiting • Dizziness • Dry mouth • Constipation • Headache • Mood disturbance	• Nausea • Vomiting • Diarrhoea • Constipation • Pancreatitis • Cholecystitis	• Nausea • Vomiting • Diarrhoea • Constipation • Abdominal pain • Headache • Dizziness	• Nausea • Vomiting • Diarrhoea • Constipation • Abdominal pain • Reflux • Pancreatitis
Mechanism of action	• Sympathomimetic amine with significant anorectic activity • Major effects on the dopaminergic and noradrenergic nervous systems • Acts as an appetite suppressant	• Potent, specific and reversible long- acting inhibitor of pancreatic lipases • Prevents complete ingestion of fat leading to faecal excretion	• Naltrexone blocks opioid-mediated pro-opiomelanocortin auto-inhibition to suppress appetite	• Stimulates glucose-dependent insulin secretion • Inhibits glucagon release and gastric emptying • Suppresses appetite centres in the brain	• Stimulates glucose-dependent insulin secretion • Inhibits glucagon release and gastric emptying • Suppresses appetite centres in the brain	• Stimulates glucose-dependent insulin secretion • Inhibits glucagon release and gastric emptying • Suppresses appetite centres in the brain

* Available at the time of publication.

† Semaglutide 1 mg (Ozempic) is TGA approved for type 2 diabetes; semaglutide 2.4 mg (Wegovy) is TGA approved for chronic weight management and to reduce the risk of major adverse CV events in people with established CV disease and a BMI of ≥27 kg/m^2 without established type 1 or type 2 diabetes; tirzepatide (Mounjaro) is TGA approved for type 2 diabetes, chronic weight management and obstructive sleep apnoea in patients with obesity.

Tirzepatide

Tirzepatide, a dual GLP-1 and gastric inhibitory polypeptide receptor agonist, is TGA approved for the treatment of T2DM and obstructive sleep apnoea, and as a chronic weight management medication in adults with obesity or overweight with at least one weight-associated comorbid condition.

In the SURPASS-2 trial, tirzepatide exhibited remarkable efficacy in a head-to-head study in people with T2DM, compared with semaglutide 1 mg once weekly. Over a 40-week duration, tirzepatide 15 mg once weekly resulted in an additional 0.45% reduction in HbA_{1c} beyond that achieved with semaglutide.[41] Furthermore, the impact on weight dynamics was equally impressive, with tirzepatide 15 mg once weekly yielding a mean percentage body weight loss of 20.9% after a comprehensive 72-week treatment course in people with obesity and without T2DM.[42] The SURMOUNT-5 trial demonstrated that tirzepatide 15 mg facilitated more weight loss compared with semaglutide 2.4 mg.[43]

Beyond glycaemic control and weight management, clinical trials have unveiled further advantages. A post hoc analysis of the SURPASS-4 trial demonstrated slower progression of CKD among individuals with T2DM and elevated CV risk.[44] In the SUMMIT trial, tirzepatide reduced the risk of worsening heart failure and CV death by 38% in people with HFpEF and obesity, almost half of whom also had T2DM.[45] Additionally, the phase 2 SYNERGY-NASH trial demonstrated that tirzepatide was superior to placebo in achieving resolution of MASH without worsening of fibrosis, with more than half of patients also showing improvement in fibrosis at 52 weeks.[46] The results of the SURMOUNT-MMO study are eagerly awaited to determine the CV protection

conferred by tirzepatide (clinical trial registration: NCT05556512). In the future, dual and triple incretin-based therapies are expected to produce more potent weight loss effects.

Implications for weight management with other hypoglycaemic agents

Sodium-glucose contransporter-2 inhibitors

Although SGLT-2 inhibitors are less effective than GLP-1RAs in reducing body weight, they play an important role in providing substantial CV protection in patients with heart failure and T2DM. SGLT-2 inhibitors have been shown to reduce the risk of composite CV death or first hospitalisation for heart failure by 20%.

Dapagliflozin and empagliflozin are PBS listed as adjunct therapy in patients diagnosed with heart failure (New York Heart Association class II, III or IV), with left ventricular ejection fraction of less than or equal to 40%.[47] Dapagliflozin and empagliflozin are also PBS listed as adjunct therapy in patients with T2DM, with CVD, at high risk of CVD or who identify as Aboriginal or Torres Strait Islander.

In patients with renal impairment (with or without T2DM), the DAPA-CKD trial showed that dapagliflozin reduced the decline in estimated glomerular filtration rate, progression to end-stage CKD and death from renal or CV causes by 39%.[48] Similarly, the EMPA-KIDNEY trial showed that empagliflozin significantly reduced the risk of kidney disease progression or CV death in a broad population of patients with CKD, including those without T2DM.[49] Both dapagliflozin and empagliflozin are PBS listed for CKD (authority required), in addition to an ACE inhibitor or angiotensin receptor blocker.

Whether using an SGLT-2 inhibitor or a GLP-1RA, metformin should always be considered as first-line therapy for T2DM to reduce insulin resistance. Although metformin is typically listed as a weight-neutral agent in patients with T2DM, it can promote modest weight loss in women with obesity and polycystic ovarian syndrome; however, it is not currently approved by the TGA for this indication.[50]

Insulin

Ideally, the management of T2DM should address the core metabolic derangements of the disease, namely insulin resistance and reduced insulin secretion. Beta cell loss is an intrinsic component of the pathogenesis of T2DM and, despite the increasing availability of alternative glucose-lowering medications, insulin may still be required to achieve adequate glycaemic control (either via direct insulin injection or through increased insulin production secondary to sulfonylureas). Although insulin can reduce the microvascular and macrovascular complications associated with poor glycaemic control, it often contributes to weight gain. Insulin stimulates lipogenesis, inhibits protein catabolism and slows basal metabolism, thereby promoting fat mass gain. In combination with the abnormal peripheral administration route of insulin, these effects lead to reductions in energy metabolism and the well-known weight gain seen with insulin-dependent diabetes.[51] Nonetheless, insulin therapy is often necessary in people with long-standing T2DM to achieve adequate glycaemic control.

Dulaglutide

Dulaglutide, a once-weekly GLP-1 RA, while not TGA approved for obesity treatment, is PBS listed for the adjuvant management of T2DM in patients who meet strict inclusion criteria (including those who are intolerant to, or not achieving a clinically meaningful glycaemic response on, SGLT-2 inhibitors). In the REWIND trial, dulaglutide significantly reduced the risk of major adverse CV events by 12%, including nonfatal myocardial infarction, stroke and cardiovascular death, even among patients without established CV disease.[52] Although the weight loss achieved with dulaglutide is modest compared to newer GLP-1RAs, its once-weekly dosing, CV benefit, and PBS accessibility make it a valuable option in the concurrent management of T2DM and obesity.

Bariatric surgery

Weight loss surgery is an important inclusion in the clinician's armamentarium for the management of obesity and T2DM. Compared with other management strategies, weight loss surgery is associated with long-term reductions in overall mortality, as well as decreased incidences of T2DM, myocardial infarction, stroke and cancer.[53] The Australian and New Zealand Obesity Society and the Royal Australian College of General Practitioners recommend considering weight loss surgery for people with a BMI greater than 35 kg/m^2 and T2DM, or people with a BMI greater than 40 kg/m^2 who are at high risk of developing T2DM when lifestyle interventions and medical therapy have been unsuccessful. The most common types of weight loss surgery in Australia are gastric bypass (mini loop or Roux-en-Y) and sleeve gastrectomy.[54] Although frequently performed in previous years, gastric banding is now uncommon due to its high failure rate and requirement for repeat procedures.

Many people with T2DM will experience improvement or normalisation of blood glucose levels after surgery, mandating close monitoring of medications in the postoperative period. These procedures do carry associated surgical and nutritional deficiency risks, with patients needing long-term monitoring of metabolic parameters, nutritional intake and bone health. Many patients who undergo weight loss surgery do experience weight regain and remain at high risk of T2DM recurrence. With the advent of potent incretin-based therapies, it remains unclear whether pharmacotherapy should be mandated prior to consideration for surgery.

Conclusion

Diabetes and obesity are two of the highest contributors to the burden of chronic disease in Australia. A multipronged approach to tackling these inter-related conditions through weight loss can target the core metabolic derangements in both and improve long-term morbidity and mortality. Lifestyle interventions paired with effective pharmacotherapy options have shown significant improvements in inducing weight loss and T2DM control. Such strategies should be considered early; ideally, before the development of comorbidities associated with T2DM and obesity. **ET**

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A list of references is included in the online version of this article (https://medicinetoday.com.au/mt/2025/august/supplements/focus-obesity-collection).

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Concurrent management of type 2 diabetes and obesity

TESSA WEIR MB BS, FRACP
SARAH GLASTRAS BSc(Hons), MB BS(Hons), FRACP, PhD

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PEER REVIEWED FEATURE

Targeting the weight within

Obesity pharmacotherapy in cardiovascular disease

JENNIFER SUN BMedSc, MD, MMed (Int Med)
JOHN J. ATHERTON MB BS, PhD, FRACP, FCSANZ, FESC

Obesity is a major contributor to cardiovascular disease and mortality. New pharmacological treatments, including incretin therapies, have shown significant weight loss and cardiovascular benefits. Large trials have demonstrated that these agents reduce cardiovascular events in patients with cardiovascular disease and improve outcomes in heart failure, kidney disease and metabolic dysfunction-associated steatohepatitis. This article reviews the cardiovascular impact of weight loss and the role of therapies such as semaglutide and tirzepatide in reducing cardiovascular disease risk.

KEY POINTS

- Obesity independently increases cardiovascular mortality, and weight loss of 5 to 10% yields meaningful reductions in cardiovascular disease risk factors; weight loss of 10% and above is associated with improved cardiovascular outcomes.
- Lifestyle interventions remain foundational, but maintaining weight loss is challenging, with most patients regaining 80% of lost weight within five years.
- Glucagon-like peptide-1 receptor agonists have demonstrated significant weight loss and cardiovascular benefits in both patients with and without diabetes, including a reduction in major adverse cardiovascular events.
- Next-generation therapies are emerging, showing promise for greater weight loss and potential cardiovascular improvements, with ongoing trials evaluating long-term outcomes.

Obesity is a major public health problem that contributes both directly and indirectly to cardiovascular disease (CVD) and mortality. In 2015, obesity was estimated to have accounted for four million deaths globally, two-thirds of which were caused by CVD.[1] The management of obesity is rapidly evolving with the introduction of new pharmacological treatments that achieve weight loss comparable to that seen with bariatric surgery. Modern pharmacological agents such as glucagon- like peptide-1 (GLP-1) receptor agonists and combination glucose-dependent insulinotropic polypeptide (GIP)/GLP-1 receptor agonists have also been shown to improve cardiovascular outcomes in patients with obesity.

Why is treatment of obesity important?

Obesity is a multifaceted disease that contributes directly and indirectly to atherosclerotic CVD, heart failure, atrial fibrillation and multiple CVD risk factors, including dyslipidaemia, type 2 diabetes, hypertension and sleep disorders (Figure). It is increasingly recognised that obesity leads to increased CVD mortality independent of cardiovascular risk factors.[2-11] Modest reductions in weight of 5 to 10% can produce clinically significant

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Dr Sun is a Cardiology Advanced Trainee in the Department of Cardiology, Royal Brisbane and Women's Hospital, Brisbane. Professor Atherton is Director of Cardiology at Royal Brisbane and Women's Hospital, Brisbane; and Professor at the Faculty of Medicine, University of Queensland, Brisbane, Qld.

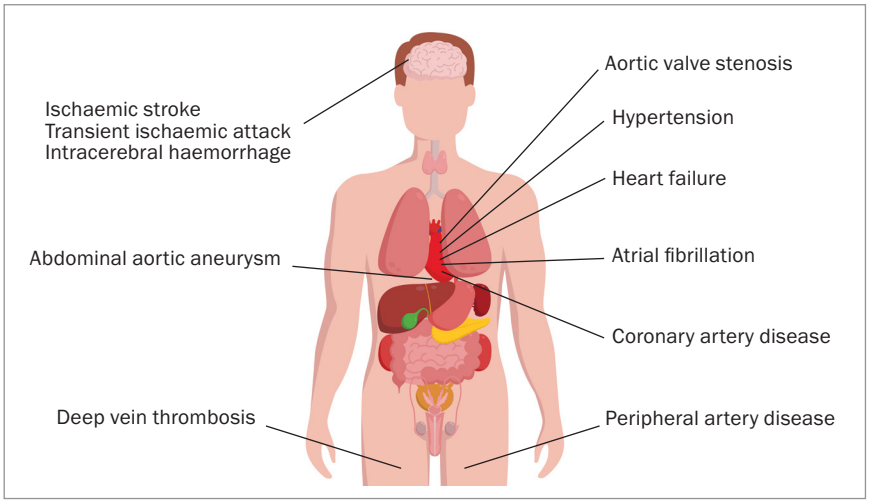

Figure. Cardiovascular diseases associated with obesity.

1. CLASSIFICATION OF OVERWEIGHT AND OBESITY ACCORDING TO BMI*†

- **Underweight:** <18.5 kg/m^2
- **Normal:** 18.5–24.9 kg/m^2
- **Overweight:** 25.0–29.9 kg/m^2
- **Grade 1 obesity:** 30.0–34.9 kg/m^2
- **Grade 2 obesity:** 35.0–39.9 kg/m^2
- **Grade 3 or severe obesity:** ≥40.0 kg/m^2

Abbreviation: BMI = body mass index.

* BMI classifications of obesity are based on the WHO classifications.

† For many Asian populations, additional trigger points for public health action were identified as ≥23 kg/m^2 representing increased risk, and ≥27.5 kg/m^2 as representing high risk. The suggested categories are as follows: <18.5 kg/m^2, underweight; 18.5–23 kg/m^2, increasing but acceptable risk; 23–27.5 kg/m^2, increased risk; and ≥27.5 kg/m^2, high risk.

improvements in CVD risk factors. Moreover, the degree of benefit in reducing CVD risk factors and improving clinical outcomes increases with higher percentages of weight loss.[9,12-15] The most widely accepted body mass index (BMI) classifications of obesity are shown in Box 1.

A systematic review and meta-analysis of randomised controlled trials evaluating weight reduction diets, with or without exercise, reported an 18% reduction in all-cause mortality over a median follow up of two years in adults with obesity.[7] Over 55% of the weighting in this meta-analysis was contributed by the LOOK AHEAD trial, which assessed whether intensive lifestyle interventions for weight loss would reduce cardiovascular morbidity and mortality in individuals with overweight or obesity and type 2 diabetes (T2DM). The intensive lifestyle intervention group achieved greater weight loss (6.0% *vs* 3.5%) and reductions in glycated haemoglobin (HbA_{1c}) as well as in all traditional CVD risk factors, except for LDL-cholesterol. However, despite the favourable effects on CVD factors, the trial did not demonstrate a significant reduction in cardiovascular outcomes. It was therefore discontinued at a median follow up of 9.6 years following a futility analysis.[11,12]

These findings suggest that although lifestyle-based weight loss interventions confer short-term benefit, it is difficult for most patients to maintain sufficient weight loss to achieve long-term reductions in cardiovascular events. Furthermore, maintaining weight loss remains a significant challenge, with up to 80% of lost weight expected to be regained over the subsequent five years.[16]

Recent developments support the growing recognition that larger degrees of weight loss (10% to 20% of body weight) may result in meaningful reductions in cardiovascular outcomes.[17,18] A post hoc analysis of LOOK AHEAD found that participants who achieved at least a 10% body weight loss in the first year had a 21% lower rate of major adverse cardiac events.[17] Similar findings have been reported in analyses of subjects who underwent metabolic surgery compared with those who did not.[11,19-23] Although these findings are derived from nonrandomised cohort studies, metabolic surgery resulting in 20 to 35% total body weight loss was associated with lower rates of all-cause mortality, cardiovascular mortality, incident heart failure, myocardial infarction and stroke (p <0.001 for all comparisons).[23]

Accordingly, metabolic surgery should be considered an important adjunct to reduce CVD risk in patients with a BMI of 40 kg/m^2 and above, or 35 kg/m^2 and above in the presence of obesity-associated comorbidities, particularly when lifestyle and pharmacological therapy alone are insufficient.[7,23]

Evidence for new pharmacologic therapy

Although lifestyle interventions remain the cornerstone of weight management, sustaining long-term weight loss is challenging. The management of obesity is evolving with the advent of pharmacological agents that produce substantial weight loss approaching that achieved with metabolic surgery.

Glucagon-like peptide-1 receptor agonists

GLP-1 is an endogenous incretin hormone produced in the intestines following food intake. It enhances insulin secretion and suppresses glucagon release. Cardiovascular outcome studies have evaluated the safety and efficacy of GLP-1 receptor agonists in patients with T2DM, with meta-analyses reporting significant reductions in major adverse cardiovascular events (hazard ratio [HR] 0.86, 95% confidence interval [CI] 0.80–0.93) without an increased risk of severe hypoglycaemia.[24] Although these studies did not specifically enrol patients with overweight or obesity, the average BMI at baseline exceeded 30 kg/m^2. This included the LEADER and SUSTAIN-6 trials, which

both demonstrated that injectable GLP-1 receptor agonists (liraglutide up to 1.8 mg once daily or semaglutide up to 1.0 mg once weekly, respectively) significantly reduced the risk of major adverse cardiovascular events in patients with T2DM who were at high cardiovascular risk.[25,26]

The STEP series of clinical trials evaluated semaglutide up to 2.4 mg once weekly in people with obesity. The STEP 1 trial showed that from baseline to week 68, the mean change in body weight in subjects without diabetes was –14.9% in the semaglutide group compared with –2.4% with placebo ($p < 0.001$).[27] The STEP 5 trial reported sustained weight loss with semaglutide out to 104 weeks.[28]

The SELECT trial was the first randomised, placebo-controlled cardiovascular outcome trial evaluating semaglutide in patients without diabetes who had overweight or obesity.[29] A total of 17,604 patients aged 45 years or older with pre-existing CVD and a BMI of 27 kg/m^2 and above (but without diabetes) were randomised to subcutaneous semaglutide once weekly (titrated up to 2.4 mg) or placebo. At a mean follow up of 39.8 months, semaglutide significantly reduced the incidence of death from cardiovascular causes, nonfatal myocardial infarction or nonfatal stroke (6.5% *vs* 8.0%, HR 0.80, 95% CI 0.72–0.90). Patients receiving semaglutide also experienced greater improvements in a variety of secondary endpoints, including reductions in body weight, HbA_{1c} level, systolic and diastolic blood pressure and high-sensitivity C-reactive protein and lipid levels.[29]

Although the reduction in cardiovascular events may be mediated through weight loss and improvements in traditional CVD risk factors (e.g. lipid levels, glycaemia, blood pressure), the early separation of event curves between the semaglutide and placebo groups even before substantial weight loss occurred suggests additional direct cardioprotective effects. This may involve modulation of inflammatory and prothrombotic pathways or other pleiotropic mechanisms.

Recent studies also report beneficial effects of semaglutide beyond cardiovascular risk reduction. At a target dose of 2.4 mg once weekly (which is TGA approved for chronic weight management), semaglutide led to significant weight loss, improved quality of life and increased six-minute walk distance in patients with obesity and heart failure with preserved or mildly reduced ejection fraction, with or without T2DM.[30,31] Notably, weight reduction in these trials was associated with reductions in NT pro B-type natriuretic peptide, suggesting beneficial effects on myocardial remodelling.

Semaglutide (aiming for a target dose of 1.0 mg weekly), which is TGA approved for T2DM) was also found to reduce the risk of clinically important kidney outcomes in patients with T2DM and chronic kidney disease (defined by either estimated glomerular filtration rate [eGFR] 50 to 70 mL/min/1.73 m^2 and urinary albumin-to-creatinine ratio >300 and <5000; or eGFR 25 to <50 mL/min/1.73 m^2 and urinary albumin-to-creatinine ratio of >100 and <5000). The primary outcome – a composite of kidney failure (dialysis, transplantation or an eGFR of <15 mL/min/1.73 m^2), at least 50% reduction in eGFR from baseline or death from kidney-associated or cardiovascular causes – was 24% lower in the semaglutide group (HR 0.76, 95% CI 0.66–0.88) at a median follow up of 3.4 years. Similar results were observed for a composite of the kidney-specific components of the primary outcome (HR 0.79, 95% CI 0.66–0.94) and for death from cardiovascular causes (HR 0.71, 95% CI 0.56–0.89). Major cardiovascular events were also reduced by 18% (HR 0.82, 95% CI 0.68–0.98).[32]

The recent phase 3 ESSENCE trial showed that semaglutide 2.4 mg once weekly improved liver histology in patients with metabolic dysfunction-associated steatohepatitis with moderate or advanced liver fibrosis. Resolution of steatohepatitis and fibrosis reduction occurred in 32.7% of semaglutide-treated patients versus 16.1% in the placebo group (estimated difference 16.5 percentage points, 95% CI 10.2–22.8).[33] Results from the STRIDE trial also found that semaglutide 1.0 mg once weekly is associated with an increase in walking distance in individuals with symptomatic peripheral artery disease and T2DM.[34]

Given the promising results of semaglutide 2.4 mg, the recent STEP-UP trial compared intensified semaglutide 7.2 mg with semaglutide 2.4 mg in adult patients with a BMI of 30 kg/m^2 and above, without diabetes. Preliminary data presented at the recent 85th Scientific Sessions of the American Diabetes Association showed that semaglutide 7.2 mg achieved a mean weight loss of 21%, outperforming the 2.4 mg dose. More than 30% of participants receiving semaglutide 7.2 mg achieved a weight loss of 25% initial body weight, or greater.[35]

Oral GLP-1 receptor agonists are also under development. A phase 3 trial found that high-dose oral semaglutide (50 mg) produced a 12.7% placebo-adjusted weight loss at week 68, comparable to subcutaneous semaglutide in patients without diabetes.[36] The recent SOUL trial evaluated the cardiovascular efficacy of oral semaglutide (up to 14 mg) in patients with T2DM (HbA_{1c} 6.5–10.0%) and established atherosclerotic CVD, chronic kidney disease (eGFR <60 mL/min/1.73 m^2), or both. The study demonstrated that oral semaglutide was associated with a lower risk of major adverse cardiovascular events (a composite of death from cardiovascular causes, nonfatal myocardial infarction or nonfatal stroke; HR 0.86, 95% CI 0.77–0.96), particularly nonfatal myocardial infarction (HR 0.74, 95% CI 0.61–0.89). However, a significant effect on major kidney outcomes was not observed (HR 0.91, 95% CI 0.80–1.05). Serious adverse event rates were comparable with placebo, although gastrointestinal events were slightly more frequent in the semaglutide group versus placebo (5.0% *vs* 4.4%).[37]

Orforglipron, an oral small-molecule, nonpeptide GLP-1 receptor agonist, has also demonstrated weight loss comparable to injectable GLP-1 receptor agonists.[38] A

phase 3 trial including adults with T2DM receiving orforglipron daily (3 mg, 12 mg or 36 mg) showed significant placebo-adjusted reductions in HbA_{1c} (–1.07%) and weight loss (–5.9%) at the highest dose.[39] There are ongoing studies evaluating the efficacy of orforglipron on weight loss and cardiovascular outcomes (clinical trial number NCT05803421; Table 1).

At the time of this publication, both subcutaneous liraglutide and semaglutide (2.4 mg weekly dose) are TGA approved for chronic weight management in Australia. This includes adults with an initial BMI of 30 kg/m^2 and above, or 27 to 29.9 kg/m^2 with at least one weight-associated comorbidity (e.g hypertension, dyslipidaemia, obstructive sleep apnoea, cardiovascular disease, prediabetes or T2DM). Liraglutide and semaglutide (2.4 mg weekly dose) are not currently subsidised under the PBS and are only available via private prescription.

Combination incretin therapies

Next-generation pharmacological treatments for obesity include combinations of GLP-1 receptor agonists with other enteropancreatic hormones (such as GIP, glucagon and amylin). These combinations may enhance weight loss and cardiometabolic outcomes beyond those achieved with GLP-1 receptor agonist monotherapy.

Glucagon-like peptide-1/glucose-dependent insulinotropic polypeptide receptor agonists

Tirzepatide is a once-weekly, subcutaneous injectable peptide with dual agonist activity at both GLP-1 and GIP receptors. GIP activation appears to act synergistically with GLP-1 receptor activation, enabling greater weight reduction than GLP-1 receptor agonism alone.[40]

In patients with T2DM, the SURPASS-2 trial compared tirzepatide with semaglutide 1 mg (both as add-on therapies to metformin) and found tirzepatide was either noninferior or superior at all doses (5 mg, 10 mg 15 mg), for both HbA_{1c} reduction and weight loss at 40 weeks. The 15 mg dose led to a mean HbA_{1c} reduction of 2.3% and a mean weight loss of 11 kg.[41]

In patients with overweight or obesity without diabetes, the SURMOUNT-1 trial showed that tirzepatide 15 mg weekly led to a mean body weight reduction of 20.9% after 72 weeks of treatment, compared with 3.1% with placebo.[42] In the recent SURMOUNT-5 trial in adult participants with obesity but without T2DM, tirzepatide (10 mg or 15 mg) achieved greater weight loss compared with semaglutide (1.7 mg or 2.4 mg weekly dose): –20.2% (95% CI –21.4 to –19.1) versus -13.7% (95% CI –14.9 to –12.6) at week 72. Tirzepatide was also associated with greater reductions in waist circumference and higher rates of achieving at least 25% weight loss.[43]

Cardiovascular outcomes data are awaited from the SURPASS CVOT trial (clinical trial number NCT04255433; Table 1) comparing tirzepatide and dulaglutide in patients with T2DM and cardiovascular disease. A recent press release reported topline results indicating that tirzepatide met the primary objective of noninferiority compared with dulaglutide for time to first occurrence of death from cardiovascular causes, nonfatal myocardial infarction or nonfatal stroke (HR 0.92, 95.3% CI 0.83–1.01), along with a reduction in all-cause mortality (HR 0.84, 95% CI 0.75–0.94).[44] Formal presentation of these findings is anticipated later this year. Meanwhile, the ongoing SURMOUNT-MMO trial (clinical trial number NCT05556512; Table 1) evaluating tirzepatide in people at high cardiovascular risk who are overweight or obese (without diabetes) is expected to report in 2027.

In the SUMMIT trial, tirzepatide significantly reduced the risk of death from cardiovascular causes or worsening heart failure events in patients with heart failure with preserved ejection fraction (ejection fraction 50% and above) and obesity (BMI 30 kg/m^2), compared with placebo (HR 0.62; 95% CI 0.41–0.95). Tirzepatide was also associated with an improved quality of life.[45]

The SURMOUNT-OSA trial reported that tirzepatide (10 mg or 15 mg) significantly reduced the apnoea–hypopnea index in people with moderate to severe obstructive sleep apnoea and obesity. Among participants using positive airway pressure, the apnoea–hypopnea index was reduced by up to 29.3 events per hour (95% CI –29.6 to –17.9), a 58.7% change from baseline, compared with a 5.3 events per hour (3.0%) reduction with placebo.[46] Tirzepatide also improved sleep-associated patient-reported outcomes.[46]

Since September 2024, subcutaneous tirzepatide has been TGA approved for the treatment of overweight and obesity. Eligible adults include those with an initial BMI of 30 kg/m^2 and above, or 27 to 29.9 kg/m^2 in the presence of at least one weight-associated comorbidity. It is also approved for the treatment of obstructive sleep apnoea in adults living with obesity.

Novel 'triple-G' agonists

Retatrutide is a novel, once-weekly injectable agent that acts on GIP, GLP-1 and glucagon receptors, and has shown promise in clinical trials for significant weight loss. In a phase 2 trial involving people with obesity, the 12 mg weekly dose of retatrutide resulted in a placebo-adjusted mean weight reduction of 22.1% after 48 weeks of treatment.[47] The phase 3 randomised controlled TRIUMPH-3 trial is currently underway to evaluate the effects of retatrutide in participants with obesity (BMI of 35 kg/m^2 and above) and established CVD, focusing on percentage change in body weight (clinical trial number NCT05882045; Table 1).

Glucagon-like peptide-1 receptor agonist and amylin analogue combinations

Amylin is co-secreted with insulin from the pancreas and contributes to postprandial satiety regulation, delays gastric emptying and inhibits glucagon secretion. Cagrilintide is a long-acting amylin analogue that, when combined with the

TABLE 1. SELECTED ONGOING RANDOMISED CONTROLLED CV OUTCOME TRIALS EVALUATING PHARMACOLOGICAL INTERVENTIONS TO ACHIEVE WEIGHT LOSS IN PATIENTS WITH OVERWEIGHT OR OBESITY

Ongoing cardiovascular outcome trials	Study population	Intervention	Primary outcome	Estimated study completion date
GLP-1 receptor agonist				
A study of daily oral orforglipron (LY3502970) compared with insulin glargine in patients with overweight at increased cardiovascular risk (ACHIEVE-4) NCT05803421	N = 2620; key inclusion criteria: adults age ≥18 years, BMI ≥25 kg/m^2, T2DM (HbA_{1c} ≥7.0% without sulfonylurea, or ≥7.5 to ≤10.5% with sulfonylurea), stable on 1 to 3 oral antihyperglycaemic drugs for least 90 days, have increased risk for CV events, stable weight (±5%) for at least 90 days	Escalated doses of orforglipron once daily *vs* subcutaneous insulin glargine once daily	Time to first occurrence of any MACE (MI, stroke, hospitalisation for unstable angina or CV death)	January 2026
GLP-1/GIP receptor agonist (tirzepatide)				
A study of tirzepatide on the reduction on morbidity and mortality in adults with obesity (SURMOUNT-MMO) NCT05556512	N = 15,374; key inclusion criteria: adults age ≥40 years with established CVD, BMI ≥27 kg/m^2	Tirzepatide once-weekly subcutaneous injection *vs* placebo	Time to first occurrence of any component of composite (all-cause death, nonfatal MI, nonfatal stroke, coronary revascularisation or heart failure events)	October 2027
A study of tirzepatide compared with dulaglutide on major cardiovascular events in participants with T2DM (SURPASS CVOT) NCT04255433	N =13,299; key inclusion criteria: adults age ≥40 years, BMI ≥25 kg/m^2, T2DM (HbA_{1c} ≥7.0 to ≤10.5%), established CVD	Tirzepatide once-weekly subcutaneous injection *vs* dulaglutide once-weekly subcutaneous injection	Time to first occurrence of composite endpoint of CV death, nonfatal MI or nonfatal stroke	Completed June 2025, results awaited
Combined GLP-1 receptor agonist/amylin analogues (cagrilintide/semaglutide)				
A research study to see the effects of cagrilinitide/ semaglutide in people living with diseases in the heart and blood vessels (REDEFINE 3) NCT05669755	N = 7000; key inclusion criteria: adults age ≥55 years, BMI ≥25 kg/m^2, established CVD	Cagrilintide 2.4 mg and semaglutide 2.4 mg *vs* placebo	Time to first occurrence of MACE (composite endpoint of CV death, nonfatal MI, nonfatal stroke)	October 2027
Glucagon and GLP-1 receptor dual agonist (survodutide)				
A study to test the effect of survodutide (BI 456906) on cardiovascular safety in people with overweight and obesity (SYNCHRONIZE-CVOT) NCT06077864	N = 4935; key inclusion criteria: adults age ≥18 years, BMI ≥27 kg/m^2 with established CVD or BMI ≥30 kg/m^2 with established CVD or CKD, and/or at least two weight-associated complications or risk factors for CVD	Survodutide once-weekly subcutaneous injection *vs* placebo	Time to first occurrence of any of the adjudicated components of the composite endpoint: CV death, nonfatal MI, nonfatal stroke, ischaemic coronary revascularisation or heart failure events	April 2026

Abbreviations: BMI = body mass index; CV = cardiovascular; CVD = cardiovascular disease; HbA_{1c} = glycated haemoglobin; MACE = major adverse cardiovascular event; MI = myocardial infarction; T2DM = type 2 diabetes mellitus.

GLP-1 receptor agonist semaglutide, has demonstrated synergistic effects. In a phase 2 trial of adults with T2DM and a BMI of 27 kg/m^2 and above, combination cagrilinitide/semaglutide achieved greater weight loss (–15.6%) at 32 weeks compared to semaglutide alone (–5.1%) or cagrilintide alone (–8.1%).[48] The phase 3 REDEFINE-3 trial will further assess the impact of cagrilinitide/semaglutide on major adverse cardiovascular events in people with obesity (with or without T2DM) and established CVD (clinical trial number NCT05669755; Table 1).

Glucagon and glucagon-like peptide-1 dual agonist

Survodutide is a dual GLP-1 and glucagon receptor agonist. In a phase 2 randomised controlled trial involving adults without diabetes and with a BMI of 27 kg/m^2 and above, survodutide administered once

2. CONSIDERATIONS FOR HEALTHCARE PRACTITIONERS MANAGING CVD IN PATIENTS WHO HAVE OVERWEIGHT OR OBESITY

- Ask permission to discuss the patient's weight in a nonjudgmental manner
- Recognise that obesity is a chronic disease that requires ongoing management and monitoring from medical and other allied healthcare professionals
- Discuss the impact of weight on health outcomes and quality of life, and the benefits of weight reduction
- Classify obesity according to BMI (with measurement of waist circumference)
- Take a history regarding current eating patterns and physical activity
- Consider underlying contributors to weight gain, including pharmacotherapy (e.g. insulin, sulfonylureas, beta blockers, antidepressants, corticosteroids, contraceptives) and metabolic conditions (e.g. hypothyroidism)
- Evaluate and manage other CVD risk factors according to guidelines
- Screen for psychological conditions (e.g. depression), obesity-associated complications and consider the contribution of cardiac disease to exercise intolerance (e.g. heart failure)
- Discuss lifestyle approaches (e.g. dietary, exercise) to weight reduction and set realistic goals, which may involve referral to allied healthcare professionals (e.g. dietician, exercise physiologist, clinical psychologist)
- Discuss pharmacological approaches to weight reduction considering limitations associated with reimbursement and supply
- Consider referral to appropriate specialists for consideration of metabolic surgery in patients with a BMI of 40 kg/m^2 or more or 35 kg/m^2 or more with obesity-associated comorbidities despite lifestyle and pharmacological therapy

Abbreviations: BMI = body mass index; CVD = cardiovascular disease.

weekly for 46 weeks led to dose-dependent weight loss. The 4.8 mg dose produced a placebo-adjusted weight reduction of 12.1%.[49] Phase 3 trials – SYNCHRONISE-1 (in people without diabetes) and SYNCHRONISE-2 (in people with diabetes) – are ongoing to assess the efficacy and durability of weight loss with 3.6 and 6 mg doses over 76 weeks (clinical trial numbers NCT06066515 and NCT06066528). The SYNCHRONISE-CVOT trial will evaluate the cardiovascular safety of survodutide in participants with overweight or obesity and established CVD, chronic kidney disease or cardiovascular risk factors (clinical trial number NCT06077864; Table 1).

Conclusion

Obesity should be recognised as both an independent CVD risk factor and a chronic disease in its own right. An evolving body of evidence shows that weight reduction improves health outcomes beyond its effect on intermediary CVD risk factors. Lifestyle interventions remain the cornerstone of obesity management, and typically involve a multidisciplinary approach with GPs, cardiologists, endocrinologists and allied health professionals. Although addressing obesity can be challenging, all healthcare professionals should ask permission to discuss a patient's weight in a sensitive, nonjudgemental manner (Box 2). Where lifestyle measures alone are insufficient, pharmacotherapy should be considered. Available options include GLP-1 receptor agonists such as semaglutide (2.4 mg weekly dose) and the dual GLP-1/GIP receptor agonist tirzepatide. Cardiovascular outcome trials evaluating novel agents that target multiple pathways – including combinations of GLP-1 agonism, GIP agonism, glucagon receptor agonism and amylin analogues – are ongoing and will help define the next generation of obesity treatments. MT

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A list of references is included in the online version of this article (https://medicinetoday.com.au/mt/2025/august/supplements/focus-obesity-collection).

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Targeting the Weight Within

Modern Solutions for Obesity

JENNIFER SUN BMedSc, MD, MMed (Int Med); **JOHN J. ATHERTON** MB BS, PhD, FRACP, FCSANZ, FESC

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