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EDUCATIONAL SERIES

Obesity and Weight-loss Management:

A Radically Different Way of Managing Chronic Metabolic Diseases

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About the expert

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Obesity is defined as "a chronic, relapsing, multi-factorial, neurobehavioral disease, wherein an increase in body fat promotes adipose tissue dysfunction, resulting in adverse metabolic, biomechanical, and psychosocial health consequences".[1] Body weight is to a large degree genetically determined, with 40–70% of the body phenotype inherited. Energy intake and expenditure are tightly regulated by a complex interaction of gut hormones and neuropeptides.

Long-term successful management of obesity is challenging. However, as detailed in this article, a moderate amount of weight loss (5–10%) is clinically meaningful and has a significant impact on obesity-associated complications. Shifting the focus from weight loss to health improvement, prevention and treatment of acute and chronic medical conditions, life lived and enjoyed in good health, and improved life expectancy, we can substantially change the clinical approach to the management of obesity.

This review discusses the assessment and management of obesity in the light of this new approach. The evidence that small but clinically-meaningful sustained weight loss, which can be achieved with medical means, can change the trajectory and outcome of many chronic conditions linked with obesity, can motivate patients and clinicians to consider medical weight management. The role of pharmacotherapy as one part of the treatment of obesity will be explored.

HIGHLIGHTS

1. 5–10% weight loss can significantly improve health and extend life expectancy.
2. An important shift from weight loss to intrinsically meaningful areas, such as improvement of health and quality of life.
3. Current best practice and international guidelines for clinical weight management.
4. Why weight loss maintenance is difficult to achieve, and how to use pharmacotherapy to achieve this 5–10% weight loss.
5. Obesity management in a NZ context – barriers and opportunities.

Background

Obesity involves interactions between genetic and environmental factors, including behavioural (diet and physical activity), socioeconomic, and cultural influences.[2,3] There has been a doubling of global rates of obesity over the last three decades.[2] NZ has the third highest adult obesity rate in the OECD,[4] with one in three adults (aged ≥15 years) classified as obese, corresponding to an estimated 1.22 million adults. Obesity is likely to be the most prevalent modifiable risk factor associated with patients' long-term health that is encountered in primary care.[5,6]

Obesity pathophysiology

Energy balance is regulated by complex neural systems and obesity is caused by an imbalance of this energy regulation.[7-9] To treat obesity successfully it is important to understand the concept of the body weight 'set-point', a genetically-determined weight range, which is maintained by a precise balance between energy intake, regulated via feeding behaviours, and energy expenditure, which is the sum of resting metabolic rate, accounting for approximately 60% of energy expenditure, and activity-based energy expenditure.[8]

Satiety and hunger hormones, such as ghrelin from the stomach, leptin from adipose tissue, and the gut hormones GLP1, CCK, PYY as well as neurotransmitters (AgRP, NPY, POMC) regulate feeding behaviour and energy expenditure to keep weight within the genetically-determined range.[2,6,7,10] Leptin, whose levels are closely related to the amount of adipose tissue, preferentially intra-abdominal fat, reflects the levels of long-term energy stores, and falling leptin levels with weight loss increase hunger and food intake, and decrease energy expenditure. This explains why weight loss with dietary means alone is frequently unsuccessful, why any weight management attempt needs to be done with a long-term view, and why medication or bariatric surgery are often required to achieve lasing success.

Triggers for weight gain

Triggers for weight gain are multifactorial and include medications that cause weight gain,[3,11] pregnancy and menopause,[12,13] or emotional and dysfunctional eating (e.g. binge eating, night-time eating), often caused by major stressful life events, or related to early childhood trauma.[14-16] Underlying depression and anxiety, which are common in people with significant obesity, can also be triggers for weight gain.

Furthermore, complications of obesity can by themselves exacerbate weight gain: untreated obstructive sleep apnoea (OSA) can lead to weight gain,[17] mechanical complications of weight such as osteoarthritis of weight-bearing joints can lead to reduced mobility,[18] and the chronic low-grade inflammation of dysfunctional intra-abdominal fat can worsen non-alcoholic fatty liver disease (NAFLD)/non-alcoholic steatohepatitis (NASH),[19] and asthma.[20] Also, rare endocrine causes (hypothyroidism, excess endogenous cortisol production, hypothalamic obesity) or childhood onset monogenic causes for obesity (Prader-Willi syndrome) need to be excluded or treated appropriately.[3]

Obesity comorbidities

Obesity places a high burden on human health because it is intrinsically linked and causative for several chronic medical conditions, notably insulin resistance and type 2 diabetes (T2D), hypertension, dyslipidaemia, cardiovascular disease (CVD), NAFLD/NASH, certain cancers (including breast, endometrial, and bowel cancer), and mechanical complications of excess weight such as osteoporosis and OSA.[2,3,10,21,22] Pathways leading to the development of some of these weight-related comorbidities are detailed in **Figure 1**.[2]

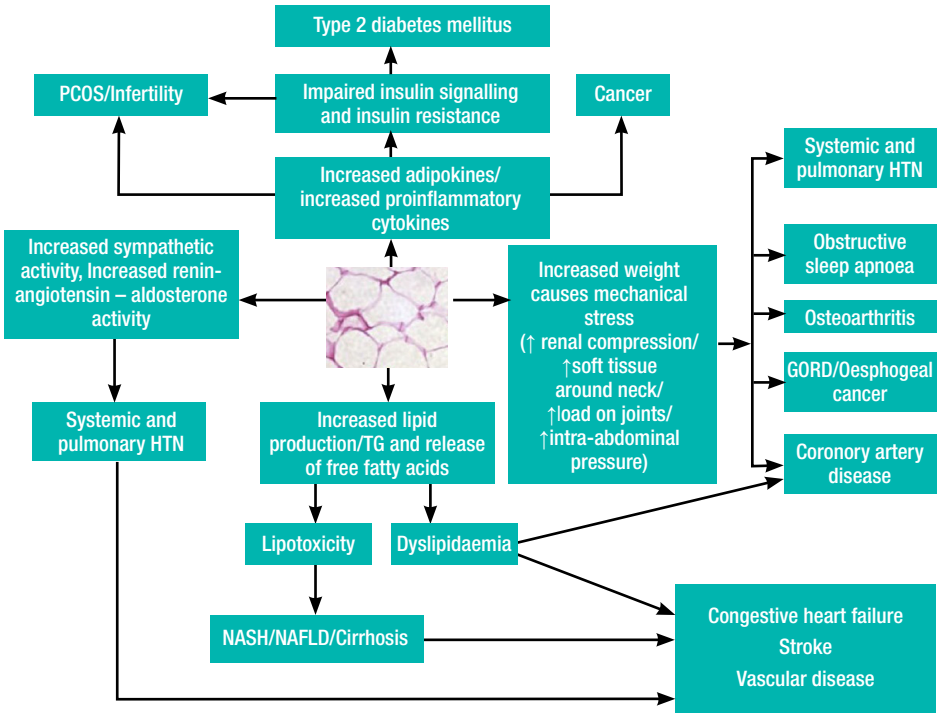

Figure 1. Pathways by which obesity contributes to the development of some common weight-related comorbidities.[2] Abbreviations: GORD = gastroesophageal reflux disease; HTN = hypertension; NAFLD = non-alcoholic fatty liver disease; NASH = non-alcoholic steatohepatitis; PCOS = polycystic ovary syndrome; TG = triglycerides.

Mortality and morbidity increase with increasing stages of obesity.[2] It has been estimated that each 5 kg/m^2 increase in BMI above 25 kg/m^2 increases overall mortality by approximately 30%, vascular mortality by 40%, and T2D mortality by 210%.[23] Life expectancy is reduced by 2–4 years at a BMI of 30–35 kg/m^2 and by 8–10 years at a BMI of 40–45 kg/m^2 (**Figure 2**). The main causes of death include ischaemic heart disease, stroke, and T2D-related complications.[2]

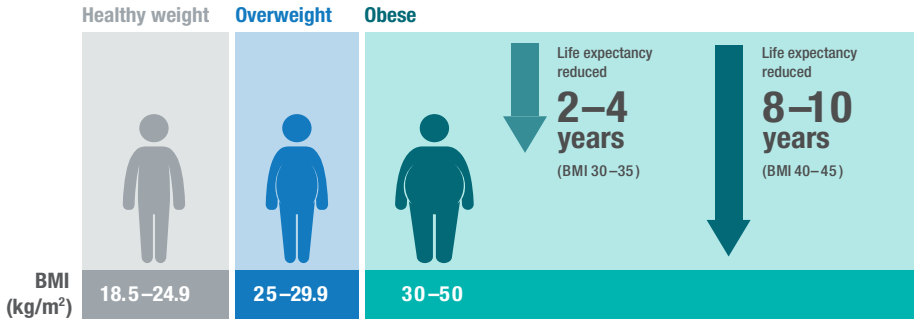

Figure 2. Effects of obesity on life expectancy.[23]

Obesity, like any other chronic disease, has a wide severity spectrum, ranging from being overweight (BMI 25–30 kg/m^2) with minimal impact on health and life expectancy, to severe end-stage disease with significant complications and shortening of life expectancy. The Edmonton Obesity Staging system (EOSS), a five-level classification system, uses obesity-related complications, functional status, and psychological impact to describe severity of obesity. Padwal *et al.* examined the ability of the EOSS in predicting mortality in a large US based sample[24] In this study, EOSS stages independently predicted mortality even after adjustment for BMI and features of the metabolic syndrome.

Clinical Practice Guidelines for the care of people with obesity published by the American Association of Clinical Endocrinologists (AACE) and the American College of Endocrinology (ACE) support this complication-focused approach by devising their own staged concept of none, mild, moderate, and severe complications of obesity, with weight loss targets and recommendations based on severity of complications, in order to encourage clinicians to assess clinical risk and to prioritise treatment, e.g. lifestyle, medication, or bariatric surgery.[25]

Furthermore, as detailed in the recent Research Review Special Report, COVID-19 and Obesity,[26] obesity is also a risk factor for poorer outcomes for many acute conditions such as infections (viral and bacterial), prolonged hospital stay, and higher in hospital mortality for conditions such as pancreatitis.

Improving weight-related comorbidities

It is now recognised that normalising weight or achieving substantial weight loss is not required to obtain health benefits. Even modest weight loss, 5–10% of baseline weight, results in improvement in cardiometabolic risk factors and is considered clinically meaningful and sufficient to obtain significant health benefits from amelioration of obesity-related comorbidities.[27-29] For example, reductions in fasting glucose and HbA1c, triglyceride level, and systolic blood pressure begins with 2–5% weight loss and improvements in diastolic blood pressure and HDL-cholesterol level begin at 5–10% weight loss (**Table 1**).[29] For improvements in OSA and NASH, 10–15% weight loss is needed to translate into clinical improvement.

A study by Magkos *et al.* helps to understand the mechanism why only a small amount of weight loss is required to significantly impact metabolic function.[30] They discovered that moderate body weight loss (5%, 11%, and 16%) was associated with disproportionate higher loss of fat mass in different compartments, e.g. 11% body weight loss caused 23% reduction of intra-abdominal adipose tissue and a 52% reduction of intra-hepatic triglycerides, confirming that intra-abdominal and intra-hepatic fat are preferentially lost. This study also demonstrated significant improvements in glucose, triglycerides, and liver function with 5% of weight loss. Using hyper-insulinaemic euglycaemic clamp studies, they showed that liver and adipose

tissue insulin sensitivity improved with 5% and muscle insulin sensitivity with 11% weight loss. Beta-cell function also improved with weight loss in a stepwise fashion.

For some conditions more weight loss is needed to achieve meaningful improvement (**Table 1**). Reassuringly, nearly all obesity-related conditions improve to some degree with weight loss, and we generally see a parallel improvement of several conditions such as T2D, OSA, and NAFLD, quality of life, depression, sexual dysfunction, or polycystic ovary syndrome. This makes weight loss the preferred primary treatment modality for several chronic diseases (e.g. recent-onset T2D with obesity and insulin resistance should be treated with weight loss and insulin sensitisers rather than with insulin). It is important that the target of treatment is not the number on the scale, but the improvement in health and obesity-related conditions.

Comorbidity or health outcome	Weight loss needed to produce improvement
Glycaemic improvement–diabetes prevention in impaired glucose tolerance	2.5% weight loss or more; maximal impact at 10%
Glycaemic improvement–type 2 diabetes	2.5% to >15%; greater weight loss associated with greater glycemic improvement; true for all BMI classes
Triglyceride reduction	2.5% to >15%; greater weight loss associated with greater glycemic improvement; true for all BMI classes
HDL increase	5% to >15%; greater weight loss associated with greater glycemic improvement; not true for BMI >40 kg/m^2
Apnoea-hypopnea index improvement in obstructive sleep apnoea	10%+ weight loss required for significant improvement
Knee pain and function in persons with osteoarthritis	5–10% improves knee functionality, speed, walk distance and pain; 10%+ required to improve IL-6 and CRP levels; knee MRI and X-ray findings do not change
Emergent knee pain prevalence	5–10% weight loss, with persistent maintenance required to prevent knee pain in individuals with obesity
Hepatic steatosis reduction	5–15%+; greater weight loss associated with greater improvement
Non-alcoholic steatotic hepatitis activity score	10%+ weight loss required for significant improvement
Impact of weight on quality of life score	5%–15%+; greater weight loss associated with greater improvement
Depression	5–10% may reduce risk for emergent depression; individuals with depression lose as much weight as non-depressed individuals
Mobility	5–10% loss attenuates mobility decline with aging
Urinary incontinence	5–10% improves symptoms in men and women
Sexual function	5–10% improves erectile function in men and sexual dysfunction in women
Polycystic ovary syndrome and infertility	Improvement in ovulatory cycles and subsequent pregnancy with 2–5% weight loss, with more weight loss producing more robust effect
Healthcare costs	In persons with diabetes 5–10% weight loss associated with reduction in hospitalisation and medication costs, but not outpatient costs
Mortality	16% weight loss (vertical banded gastrectomy) associated with reduction in all cause and cardiovascular mortality. 5–10% weight loss with lifestyle intervention had no effect on major cardiovascular outcomes, but in those with 10%+ weight loss, there was a reduction in those outcomes

Table 1. Modest weight loss results in clinical improvement of many weight-related comorbidities.[29]
Abbreviations: BMI = body mass index; HDL = high-density lipoprotein-cholesterol; IL-6 = interleukin-6; CRP = C-reactive protein; MRI = magnetic resonance imaging.

Barriers to treatment for obesity

As the likely first point of contact for patients with obesity,[31,32] primary care practitioner awareness of the potential barriers to patients being able to access effective weight-loss treatment is important.

Disease perception factors

People carrying weight are often stigmatised by the incorrect perception held by many, including healthcare providers, that obesity is caused mainly by lack of individual will power leading to poor dietary choices and physical inactivity.[2] Reassuringly, obesity is now recognised as a chronic disease with multiple contributing factors, including many that are beyond an individual's' control.[2,33]

Practitioner factors

The complex pathophysiology that drives obesity in susceptible individuals makes weight loss management challenging and time-consuming.[34] Limited time, lack of knowledge and training, and the challenge of raising the delicate topic of a patient's weight are key reasons for primary care practitioners not initiating weight lost treatment and not following guidelines for management of obese patients.[5,6,35,36]

Patient factors

Having a low level of concern about the effects of obesity on their future health or believing that managing their disease is their own responsibility are potential barriers to people with obesity accessing treatment.[33,37] In addition, social, situational, cognitive, and emotional obstacles challenge the long-term maintenance of weight loss.[38] Many other cultural and socioeconomic factors play a role in accepting obesity treatment, as shown in a study by Taylor *et al.*,[39] evaluating attrition from publicly-funded bariatric surgery programme, that two of three European women but fewer than one in seven Pacific men proceeded to fully-funded bariatric surgery.

Pharmacotherapy perception factors

Even though pharmacotherapy can help people to lose weight, barriers to the widespread use of weight-loss medication exist, often because of concerns about medication safety, efficacy, and cost.[40-42] A lack of formal training in obesity pharmacotherapy and general discomfort with using weight-loss medications are reasons why some healthcare providers may be reluctant to employ pharmacotherapy.[41]

Overcoming inertia

Awareness about these factors, experience with successful weight management, and ongoing education of providers can be helpful to overcome clinical inertia. It is equally important to treat clinical weight management with a scientific and evidence-based approach.

Weight management guidelines

The foundation of weight-loss management is lifestyle modification.[25,32,43,44] Lifestyle modification requires a lifelong commitment to maintaining a healthy diet and increased physical activity, supported by behavioural counselling. However, up to one-third of patients with obesity do not respond to lifestyle modification alone,[45,46] and many struggle to sustain weight loss gains over the long term.[47,48] Hence, adjunctive therapies to lifestyle modification, pharmacotherapy and metabolic surgery, have an important role to play in weight-loss management.

The addition of pharmacotherapy to lifestyle modification produces greater weight loss and weight-loss maintenance than lifestyle modification alone.[25,44] Weight management guidelines, including the NZ clinical guidelines for weight management in adults,[32] recommend that pharmacotherapy should be used as an adjunct to lifestyle modification to help patients who struggle with lifestyle modification alone.[32,43,44] The NZ clinical guidelines for weight management in children do not recommend the use of weight-loss drugs in children aged <12 years.[49]

Weight management guidelines generally recommend adjunctive weight-loss medication for people with a BMI of ≥30 kg/m^2 or BMI ≥27 kg/m^2 with one or more comorbid conditions.[32,44] An algorithm of when to initiate adjunctive weight-loss pharmacotherapy for patients with obesity as well as patients with obesity and comorbidities that can be ameliorated by weight loss is depicted in **Figure 3**.[25]

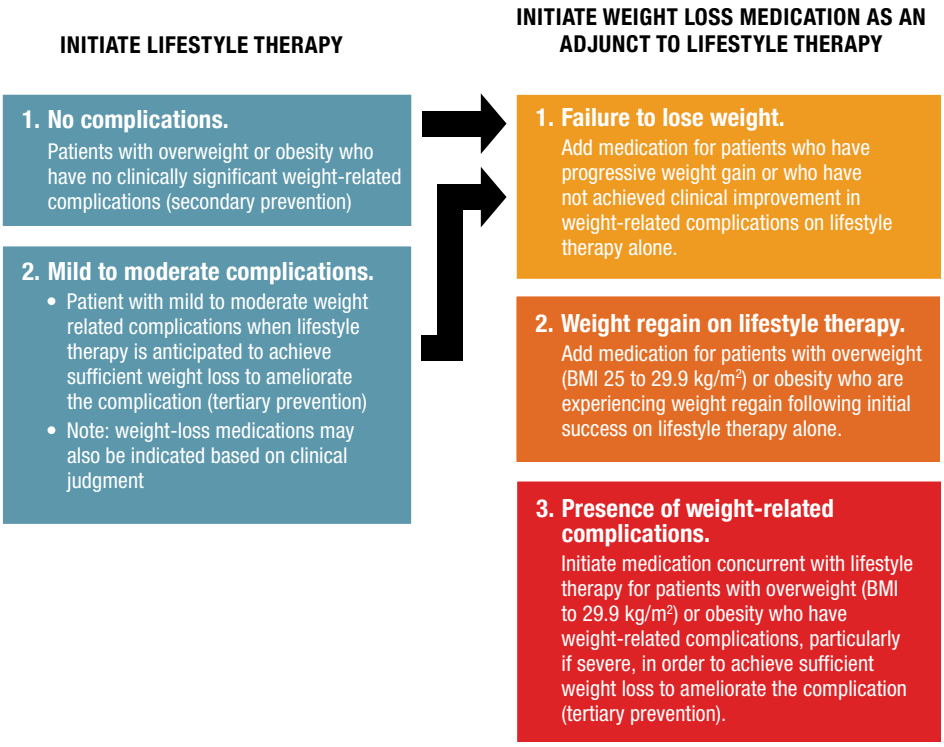

Figure 3. Algorithm for when to commence weight-loss pharmacotherapy in patients with obesity with or without weight-related complications.[25]

Metabolic surgery is an effective weight loss intervention for select, motivated patients who are able to maintain lifelong dietary and other lifestyle changes. In general, guidelines recommend metabolic surgery as an adjunct to lifestyle modification in patients with a BMI >40 kg/m^2 or ≥35 kg/m^2 with one or more comorbidities.[25,32,43,44] In NZ, access to the publicly-funded procedure is restricted by referral criteria and determination of which people will gain the greatest benefit from surgery.[32]

Approach to medical weight management and the rationale for use of pharmacotherapy

Clinical weight management needs to start with a thorough assessment, including medical and weight history, comorbidities, contributing factors, age of onset and family history as well as severity of the obesity. A treatment plan needs to include nutrition and lifestyle measures, exercise prescription, behaviour change and adjustment, and assessment of medications, those that may cause weight gain and possible weight-management medications.

It is inappropriate to prescribe a weight management medication without a long-team treatment plan, and pharmacotherapy should be seen as an adjunct to lifestyle modification, just as it is for managing other chronic diseases such as hypertension, diabetes, and CVD.[50]

Weight loss secondary to lifestyle changes can lead to metabolic adaptations that increase appetite and reduce energy expenditure hence promoting weight regain.[40,51,52] As it is difficult to overcome physiology with behaviour, weight-loss medications, which alter the physiology of bodyweight regulation, help to increase the likelihood of long-term success.[52]

Tailoring pharmacotherapy

Three weight-loss medications, phentermine, orlistat, and liraglutide, are registered as adjunctive treatments for weight loss in NZ (**Table 2**).[53-55] In Australia, the combination of naltrexone and bupropion has recently been licensed. This medication is also available in Europe, the UK, and, the US. The combination of phentermine and topiramate has been approved by the FDA in the US; however, neither of these medications are currently licenced in NZ.

The success of pharmacotherapy in the management of obesity is dependent on tailoring treatment to patients' behaviours, preferences, and comorbidities, as well as clinical monitoring of efficacy and tolerability.[56,57] Ideally, a medication has dual benefit for improvement of a condition *per se* and weight loss. For example, liraglutide and other GLP-1 agonists help with weight management and glycaemic control. The diabetes medications dapagliflozin or empagliflozin (SGLT2 inhibitors) improve diabetes control, heart failure, and renal function, and help with weight loss.

Knowledge of weight-loss medications, including their mechanisms of action, efficacy and tolerability profiles, and limitations of use in specific patient groups (**Table 2**), informs the decision of whether pharmacotherapy is appropriate in the management of a patient with obesity and which medication to use.[50] For example, phentermine might be the best option for patients with excessive appetite and liraglutide would provide glycaemic control in addition to weight loss for patients with pre-diabetes. Orlistat and liraglutide might be the preferred options for patients with hypertension or other pre-existing medical complications such as CV disease or with contraindications for centrally-acting medications (e.g. depression and anxiety).[25,50,58] It is important to know which weight-loss medications can be combined for dual benefit, e.g., an SGLT2 inhibitor, which can increase hunger and carbohydrate cravings, and phentermine, an appetite suppressant, have synergistic effects on weight loss.

Cost may also be a factor in the selection of a weight-loss medication, and a reason for stopping treatment and hence preventing long-term use.[50,57] None of the three weight-loss medications approved for use in NZ is subsidised by PHARMAC (**Table 2**). At least in the setting of the US healthcare system, phentermine was determined to be the dominant weight-loss strategy after 1, 3, and 5 years in a cost-effectiveness analysis of six weight-loss medications and intensive lifestyle modification for people with mild obesity (BMI 30–50 kg/m^2).[59] Drug acquisition cost was the main determinant of whether or not a strategy was cost effective.

	Phentermine	Orlistat	Liraglutide
Mechanism	Suppression of appetite primarily via increased CNS noradrenaline activity	Inhibition of fat digestion and absorption via inhibition of gastric and pancreatic lipase	Suppression of appetite via increasing feelings of satiety and fullness and reducing feelings of hunger Acts on glucose homeostasis to lower fasting and post-prandial glucose
Standard dose	15 or 30 mg once daily	120 mg three-times daily	0.6–3.0 mg once daily
Administration route (form)	Oral (capsule)	Oral (capsule)	Injection (subcutaneous)
Placebo-subtracted weight loss (kg)	3.6 kg (at 6 months)	2.9–3.4 kg (at 1 year)	5.8 kg (at 1 year)
Common adverse events	Tachycardia, palpitation, hypertension, precordial pain, dry mouth, insomnia	Faecal urgency, faecal incontinence, oily stools, flatulence	Nausea, diarrhoea, constipation, vomiting Rare: cholecystitis, pancreatitis
Available in NZ	Yes	Yes	Yes
PHARMAC subsidy	No	No	No
Cost	$100 per month	$150 per month	$500 per month

Table 2. Summary of the main features of the weight-loss medications approved as adjunctive treatments for management of obesity in NZ.[44,50,53-55]

Stopping pharmacotherapy

Weight-loss medications should be stopped if safety or tolerability issues arise and/or weight loss of >5% of initial body weight is not achieved after 3–4 months.[34,43,44,50] In cases where <5% weight is achieved or side effects are experienced, an alternative medication or treatment approach should be considered. If a medication is well tolerated and >5% weight loss has been achieved after 3–4 months, pharmacotherapy should be continued for as long as there are clinical benefits, including absence of significant weight regain.[34,43]

Long-term pharmacotherapy

With obesity now considered a chronic disease, weight-loss management is evolving to favour long-term therapy.[42] Obesity requires ongoing treatment due to weight loss being challenging to achieve and maintain.[50,58]

Pharmacotherapy can facilitate long-term weight maintenance and limit weight regain in people being treated for obesity,[34,50] and no safety signals indicating that any of the currently-available weight-loss medications are unsuitable for long-term use have emerged to date.[50]

Historically, phentermine was typically used for short-term use but this is incongruous with obesity being a chronic disease requiring long-term management.[50] Long-term phentermine use does not seem to be associated with serious side effects and its dependency potential appears to be low.[42,50] An analysis of data from a large electronic health record cohort (n=13,972) in the US found greater weight loss without increased risk of CVD or death in overweight or obese patients using phentermine for longer than 3 months and up to 3 years.[42]

Based on evidence, if pharmacotherapy has produced weight loss and health improvement it should be continued as long as the benefit outweighs the risk.[34,50] This approach is similar to the way that antihypertensive and antidiabetic medications, if well tolerated and effective, are continued even after blood pressure or glycaemic control has reached target.[50] In NZ, it is important to discuss and document longer-term use of weight-loss medication with your patient, phentermine use can be continued beyond 12 weeks provided continued monitoring of the patient occurs (for weight loss and medical conditions) and for as long as weight loss is maintained.[53] We have limited cardiovascular outcome data beyond 2 years of continued treatment, and an exit strategy, including tailored reduction of weight-loss medication, needs to be discussed from the outset.

Pharmacotherapy after surgery

Metabolic surgery is an effective treatment for persons with moderate (BMI 35–39.9 kg/m^2) and severe obesity (BMI ≥40 kg/m^2).[60] However, inadequate weight loss and even weight regain are possible in patients who undergo metabolic surgery.

Patients who received weight-loss medication after metabolic surgery have been shown to achieve additional weight loss benefit, indicating that pharmacotherapy is a useful tool for patients with inadequate weight loss or weight regain after metabolic surgery.[60,61] Patients were statistically significantly more likely to lose ≥5% of their total weight with the use of adjunctive weight-loss medication. Commencing weight-loss medication at the post-surgery nadir weight appears to result in a greater amount of total weight loss from the pre-operative period.

TAKE HOME MESSAGES

- Obesity is a chronic disease and should be acknowledged and treated as such.
- Obesity and weight-related comorbid diseases are responsible for substantial morbidity and mortality.
- Barriers to accessing treatment for obesity include a lack of physician time and training and the false assumption that obesity is due to a lack of individual will.
- **Modest weight loss of 5–10% results in improvements in weight-related comorbidities.**
- Thorough history taking and evaluation for weight-gaining medication is necessary.
- Lifestyle modification is the foundation of weight-loss management, and counselling or psychological interventions may be necessary.
- Stepping up care via the addition of weight-loss pharmacotherapy or metabolic surgery is recommended for patients who struggle on lifestyle modification alone.
- Changing the paradigm and focusing on improvement of chronic conditions rather than weight loss may change the hesitancy in patients and clinicians to accept medical weight management.
- Long-term pharmacotherapy to facilitate weight loss or prevent weight regain is consistent with obesity being a chronic disease.
- Pharmacotherapy that has been successful should be continued as long as is the benefits outweigh the risks of treatment.
- Pharmacotherapy is a useful adjunct to metabolic surgery in patients with inadequate weight loss or weight regain after surgery.

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