Pharmacotherapy for obesity

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Background

Obesity is a serious, chronic, relapsing disease of energy regulation, with strong genetic and early-life environmental determinants. Pharmacotherapy can be a useful adjunct to lifestyle intervention in effecting and maintaining clinically meaningful weight loss.

Objectives

The aim of this article is to discuss the role of pharmacotherapy in obesity management. The efficacy, side effects and contraindications of available weight-loss medications are reviewed.

Discussion

Long-term pharmacotherapy options, which can be effective in providing moderate weight loss, are available to treat obesity. Pharmacotherapy should be considered an adjunct to lifestyle intervention in those with a body mass index (BMI) >30 kg/m^2, or in those with a BMI of 27–30 kg/m^2 and obesity-related complications. Safety and efficacy should be monitored closely on commencement, and the medication should be discontinued if there are safety or tolerability issues, or if <5% weight loss is observed after three to four months.

Obesity is a serious, chronic, relapsing disease of energy regulation with strong genetic and early-life environmental determinants.[1,2] For the majority of patients, following an exemplary diet and exercise recommendations provide only modest weight loss that is difficult to sustain.[3] Similarly to the treatment of other chronic diseases, we need tools beyond lifestyle interventions to deliver better health outcomes.

Pharmacotherapy currently plays a major role in managing diseases of dysregulation, including hypertension, type 2 diabetes mellitus (T2DM), dyslipidaemia and cancer. Indeed, we have a responsibility to provide appropriate care for these common complications of obesity. The low uptake of all effective therapies beyond lifestyle interventions for weight management would be unacceptable for other chronic diseases. We need a more proactive approach to treat obesity, especially for those who are clinically severely obese, with a focus on psychological, physical and metabolic complications. Weight loss is the most logical, broadly effective and commonly sought outcome by patients with obesity.

Who should be considered for pharmacotherapy?

The goals in managing chronic disease are patient-centric, with an informed patient being able to make choices to improve health outcomes. For patients who are obese, the benefits of high-quality diet, physical activity and behavioural change do extend well beyond what may be frustratingly small changes on the scales and, as such, lifestyle management remains the foundation for improved health outcomes. Pharmacotherapy for weight management should be seen as an adjunct to lifestyle intervention, just as it is for managing hypertension, diabetes and cardiovascular disease, not as a replacement. Drug therapy acts physiologically by altering energy regulation, usually by reducing appetite, providing satiation with a smaller meal, and more prolonged satiety following the small meal. Naturally, all medications have their risks and side effects and, as clinicians, we are always weighing the risks and benefits of therapy with the risks and severity of the disease.

Body mass index (BMI), when adjusted for age and sex, is generally an excellent measure of percentage body fatness in

the population.[4,5] BMI is an accepted measure to screen for the health risks of obesity and provide cut-off points as indication for more intensive therapies. Weight-loss pharmacotherapy should be considered for patients with a BMI >30 kg/m^2, or those with a BMI of 27–30 kg/m^2 with obesity-related complications.[6–8] Lower BMI thresholds (BMI >27 kg/m^2, or BMI >25 kg/m^2 with obesity-related complications) should be considered in Aboriginal and Torres Strait Islander and Asian populations. Orlistat, phentermine and liraglutide have been approved by the Therapeutic Goods Administration (TGA) for the treatment of obesity in Australia, and topiramate is an effective off-label agent that is currently available for the management of epilepsy and migraine.

Weight-loss pharmacotherapy

Phentermine

Phentermine is a sympathomimetic agent that suppresses appetite. Analysis of randomised controlled trials (RCTs) indicates weight loss at six months of 3.6 kg, compared with placebo.[9] More recently, phentermine 15 mg was shown to induce a weight loss of 4.5 kg over placebo after six months of therapy (Table 1).[10] Phentermine is available in a slow-release resin preparation in doses of 15, 30 and 40 mg, and given as a single daily dose early in the day. Starting with 15 mg and grading up as needed reduces early cessation because of predictable, generally mild, sympathomimetic effects of dry mouth, insomnia, agitation, constipation and tachycardia. Using the lowest effective dose also reduces risks of side effects.

Given the effects of phentermine on the cardiovascular system, it should not be used in patients with a history of cardiovascular disease. Other contraindications include anxiety disorders, hyperthyroidism, history of drug or alcohol abuse or dependence, concomitant treatment with monoamine oxidase inhibitors, pregnancy and breastfeeding. It should be used with caution in patients with hypertension, history of cardiac arrhythmias, or seizures.[11] Careful monitoring of blood pressure should be performed while the patient is on phentermine.

Phentermine has been the most commonly used weight-loss management medication in Australia and the US for decades.[12] Historically, it has been approved as a short-term therapy, but for treating obesity, a chronic condition, this is illogical. Phentermine has now been studied over a two-year period in combination with topiramate,[13] and the combination is approved for long-term use by the US Food and Drug Administration (FDA).[7] The same combination has also been studied in Australia.[14] In addition, the addiction potential of long-term phentermine use is low,[15] and there is minimal evidence that long-term phentermine monotherapy is associated with serious side effects.[7] The TGA product label recommends careful evaluation before and at three months of use. Further use is at the discretion of the practitioner in conjunction with the patient. It may be reasonable to prescribe phentermine long term, provided the following criteria are met:[7,16]

- low-to-intermediate cardiovascular risk with no evidence of serious cardiovascular disease
- no serious psychiatric disease or history of substance abuse
- no clinically significant increase in pulse or blood pressure while taking phentermine
- close monitoring – monthly during dose escalation and at least every three months thereafter
- efficacy–safety stopping rule (described below) is followed.

Orlistat

Orlistat inhibits pancreatic and gastric lipases and thus reduces absorption of dietary fat. It is the only approved weight-loss medication that does not work primarily by suppressing appetite, and has a relatively good long-term safety record. Taken in a dose of 120 mg three times a day with meals, approximately 30% of oral fat intake is excreted in the stool. A mean weight loss of 2.9–3.4% is observed after one year of orlistat.[7] Side effects are due to fat malabsorption and include steatorrhoea, oily spotting, flatulence with discharge, faecal incontinence, fat-soluble vitamin deficiencies and calcium oxalate kidney stones.

Gastrointestinal side effects, the main reason for discontinuing therapy, can be reduced by adhering to a low-fat diet and increasing dietary fibre. In individuals with T2DM, improvements in glycated haemoglobin (HbA1c) of 0.4% were also observed with orlistat, compared with controls.[17] The XENical in the prevention of Diabetes in Obese Subjects (XENDOS) study found that orlistat reduces the incidence of T2DM by 37% over four years when added to lifestyle therapy in patients who are obese.[18]

Liraglutide

Liraglutide is a glucagon-like peptide-1 (GLP-1) agonist initially used to treat T2DM, and controls hyperglycaemia without causing hypoglycaemia or weight gain. Its side effect profile of decreased appetite, reduced energy intake and subsequent weight loss has led to its more recent approval as a weight management drug. A large RCT has found that liraglutide 3 mg leads to 5.6 kg (5.4%) weight loss over placebo after one year.[19] There were corresponding improvements in cardiometabolic risk factors, including inflammatory markers, glycaemic parameters, blood pressure and lipid levels.

Liraglutide was recently approved in Australia for weight management as an adjunct to diet and physical activity. It can be given independently of meals, as a subcutaneous injection into the abdomen, thigh or upper arms. The starting dose of liraglutide is 0.6 mg once daily. The dose should be increased to 3 mg in increments of 0.6 mg, with intervals of at least one week to improve gastrointestinal tolerability. Lower doses can be continued if effective when there are gastrointestinal tolerance issues with higher doses.

Common side effects of liraglutide are gastrointestinal in nature, including nausea, vomiting, diarrhoea, constipation and

dyspepsia, which can be mitigated by gradual dose escalation. Most gastrointestinal symptoms are mild to moderate, transient and diminish within days or weeks with continued treatment. Liraglutide-induced weight loss is associated with an increased incidence of symptomatic gallstones and, more rarely, pancreatitis. Patients should be warned about these conditions. Liraglutide should not be used in those with severe renal insufficiency (including end-stage renal failure), hepatic insufficiency, pregnancy, past history of pancreatitis or major depression, or psychiatric disorder.

Currently, liraglutide appears to have the strongest evidence base for cardiovascular safety, although most studies looked at its effect as an antidiabetic agent, using a lower dose. Liraglutide may be well suited as a weight-loss agent for those at high cardiovascular risk, or with glucose intolerance such as T2DM or pre-diabetes. Drawbacks include high costs (about $380/month in Australia) and gastrointestinal side effects that may limit its use.

Off-label pharmacotherapy

Several medications that are not approved by the TGA for weight loss are used off-label in Australia to treat individuals with obesity when other medications are ineffective or contraindicated. Thorough knowledge of side effects, precautions and contraindications of these medications is essential and we caution against their prescription by practitioners without expertise in obesity management. Risks and benefits of off-label use should also be discussed with the patient and clearly documented.

Topiramate

Topiramate is an anticonvulsant used to treat seizures and for migraine prophylaxis. It is also used off-label to treat obesity because of the side effect of weight loss. Several meta-analyses have estimated that 3.4–5.0 kg weight loss can be expected with topiramate monotherapy.[20,21] Effective doses range between 25 and 100 mg daily. Side effects are dose-dependent and commonly include paraesthesia, dry mouth, constipation, altered taste sensation, insomnia and dizziness.[22] Dose-related cognitive side effects include psychomotor slowing, decreased concentration and attention, memory impairment and language difficulties.[22] Rare but serious side effects include closed-angle glaucoma and increase in suicidal thoughts or ideations. Topiramate should not be used in pregnancy or in individuals with a history of glaucoma or renal stones.

Table 1. Pharmacotherapy used in obesity management in Australia[7]

Drug	Starting dose	Available doses	Weight loss versus placebo (% or kg)	Side effects	Contraindications
Phentermine	15 mg	15, 30, 40 mg	3.6–4.5 kg at six months	Dry mouth, insomnia, agitation, constipation, and tachycardia	Severe hypertension, cardiovascular disease, glaucoma, history of drug or alcohol abuse, monoamine oxidase inhibitors, selective serotonin reuptake inhibitor use, pregnancy
Orlistat	120 mg TDS	120 mg	2.9–3.4% at one year	Steatorrhea, oily spotting, flatulence with discharge, faecal incontinence, fat-soluble vitamin malabsorption	Pregnancy
Liraglutide	0.6 mg	0.6–3.0 mg	5.4% at one year	Nausea, vomiting, diarrhoea, constipation Rare: Pancreatitis, cholecystitis	Severe renal or hepatic insufficiency, pregnancy, past history of pancreatitis and major depression or psychiatric disorder
Off-label pharmacotherapy (not approved by Therapeutic Goods Administration for weight loss)					
Topiramate	12.5 mg mane	25, 50, 100 mg	3.4–5.0 kg	Paraesthesia, dry mouth, constipation, altered taste sensation, insomnia, dizziness, cognitive effects Rare: Closed angle glaucoma, depression or suicidal ideation	Glaucoma, renal stones, pregnancy (if used for weight loss)
Phentermine (Phe)/ topiramate (Top)	Phe: 15 mg mane Top: 12.5 mg mane	Phe: 15 mg Top: 12.5, 25, 50, 100 mg	5.0–6.6% at one year	Side effects of phentermine and topiramate	Contraindications to phentermine or topiramate

Table 2. Common antidiabetic drugs and their effects on body weight[7,32]

Produces weight loss (mean weight loss)	Are weight neutral	Causes weight gain (mean weight gain)
Metformin (0.6–1.2 kg)	Acarbose	Insulin (1.5–3 kg)
Glucagon-like peptide-1 (GLP-1) receptor agonists (eg exenatide, liraglutide; 1.8–2.5 kg)	Dipeptidyl peptidase-4 (DPP-4) inhibitors (eg sitagliptin, linagliptin, vildagliptin)	Sulfonylureas (eg glipizide, gliclazide, tolbutamide; 2 kg)
Sodium-glucose cotransporter 2 (SGLT-2) inhibitors (eg canagliflozin, dapagliflozin, empagliflozin; 1.8–2.7 kg)		Metiglinides (eg repaglinide; 1.8 kg)
		Thiazolidinediones (eg pioglitazone; 2.6 kg)

Phentermine/topiramate combination

Fixed-dose combinations of phentermine/topiramate are approved in the US to treat obesity. Phase 3 RCTs found weight reduction of 5.1–10.5% and improvement in metabolic parameters with the combination (Table 1).[23,24] An Australian study examined the combination of phentermine 15 mg and topiramate 25 mg for weight maintenance after initial weight loss with very low energy diets (VLEDs).[14] Forty per cent of patients in the study could not tolerate the combination, primarily because of side effects from topiramate. In the cohort that tolerated the combination, further weight loss of 5% (6.7 kg) was observed after a mean duration of 22 months.

Other medications

Two other weight loss medications approved in the US but not available in Australia include a naltrexone/bupropion combination and lorcaserin. The combination of an opioid antagonist (naltrexone) and a dopamine and noradrenaline re-uptake inhibitor (bupropion) has been shown to provide average weight loss of 4.8% after one year.[25] Common side effects include nausea, vomiting, headache, dizziness and dry mouth.

Lorcaserin, a selective 5-hydroxytryptamine (5-HT) 2C receptor agonist, suppresses appetite, with expected weight loss of 3.6% at one year.[26] Common side effects include upper respiratory tract infections, headache, dizziness, nasopharyngitis and nausea. Unlike non-selective 5-HT receptor agonists (eg fenfluramine), the incidence of cardiac valvulopathy was not increased with lorcaserin.[26]

Efficacy–safety stopping rule

On commencement of weight-loss medications, patients should be reviewed closely for the first three months (four months for medications such as liraglutide and topiramate that require gradual dose escalation) to assess safety, tolerability and efficacy. The medication should be stopped immediately should any safety or significant tolerability issues arise. There is significant variability in individual responses, with regard to weight loss, to these medications. Weight loss at 12–16 weeks predicts later weight loss at one year and beyond.[12] Sustained weight loss of 5% leads to significant improvement in obesity-related comorbidities.[6] Therefore, if the patient's response is insufficient (weight loss <5% at three to four months) despite optimisation of adherence and dose, the medication should be stopped, as the long-term benefits are likely to be outweighed by the risks and costs of treatment (Case). This sound approach has some exceptions, as pharmacotherapy is often best used to maintain weight loss following intensive dietary therapy (eg VLED), placement of intragastric balloons or even after bariatric surgery.[11,27] In these instances, satiety and limiting weight regain would be an indication for continued therapy. In addition, if one agent is not performing adequately, adding a second agent would provide an alternative clinical approach, with an additional 12–16 week assessment made.

Pharmacotherapy for patients with obesity and T2DM

There is strong evidence to suggest that obesity management is beneficial for the treatment of T2DM.[8] Table 2 summarises the common antidiabetic agents used, based on their effects on body weight. In the absence of contraindications, metformin should be used as first-line therapy for T2DM as it is safe, effective, inexpensive, and may reduce cardiovascular events and death.[28] If combination therapy is needed, or if metformin is contraindicated, the weight profile of second-line medications should be carefully considered. Whenever possible, medications chosen should promote weight loss or be weight neutral.

Several recent cardiovascular outcome trials have reported positive data on patients with T2DM at high cardiovascular risk. The Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes (EMPA-REG) trial has found that empagliflozin, a sodium–glucose co-transporter 2 (SGLT-2) inhibitor, significantly decreased cardiovascular events by 14% (10.5% versus 12.1% with placebo) and cardiovascular death by 38% (3.7% versus 5.9% with placebo) after 3.1 years.[29] More recently, the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial found that liraglutide reduced cardiovascular events by 13% (13.0% versus 14.9% with placebo) and cardiovascular death by 22% (4.7% versus 6.0% with placebo) after median follow-up of 3.8 years.[30] The cardiovascular safety and favourable weight profile of these antidiabetic agents provide an attractive option for individuals with obesity and T2DM, especially for those at high cardiovascular risk.

Pharmacotherapy for long-term use

Despite the efficacy of pharmacotherapy in producing weight loss, drugs used for weight loss are often discontinued. Reasons for cessation of therapy include costs, concerns regarding side effects and the perception that the medication is no longer necessary as a sufficient amount of weight is lost.[31] On the contrary, if therapy is well tolerated and effective, it should be continued, similarly to the way antihypertensive and antidiabetic medications are continued even after blood pressure or glycaemic control is at target. This reflects the fact that obesity is a chronic disease that requires sustained treatment, with pharmacotherapy playing an important role in promoting long-term weight maintenance and limiting weight regain.

Perhaps one of the reasons contributing to the treatment inertia in commencing or continuing pharmacotherapy to treat obesity is the concern regarding long-term adverse effects, especially cardiovascular and mental health safety. The unease is understandable given the safety issues that have led to the withdrawal of anti-obesity agents in the past (eg fenfluramine, sibutramine, rimonabant). To date, there have not been any safety signals that have emerged to suggest that any of the currently available medications are not suitable for use in the long term. Large cardiovascular outcome studies are currently being conducted for the newer medications (eg phentermine/topiramate combination, lorcaserin, naltrexone/bupropion) and should provide further long-term safety data as these become available.

Conclusion

Understanding of the various weight-loss medications available, indications, common side effects and limitations in specific patient populations allows general practitioners (GPs) to decide if, and which, pharmacotherapy is appropriate when managing patients with obesity. If used, these medications should be stopped if there are safety or tolerability concerns, or if clinically meaningful weight loss (>5%) is not achieved. Similarly, if the medication produces satisfactory weight loss and is well tolerated, it should not be discontinued empirically. Rather, medications reinforce lifestyle management and play a useful role in long-term management of obesity. By widening the repertoire in their toolbox, GPs can increase the probability of identifying a combination of treatment options that can help their patients manage overweight and obesity.

Case

Sally, 34 years of age, had been attending your practice for many years. She had a past medical history of obesity, hypertension, dyslipidaemia and polycystic ovary syndrome. Her medications included amlodipine 10 mg daily, perindopril 8 mg daily and atorvastatin 40 mg daily.

Sally had previously tried to lose weight with lifestyle interventions, including VLEDs and structured exercise programs, and achieved modest weight loss of 5 kg, which was not sustainable. She was single and her job involved administrative work in a mostly sedentary environment. On clinical examination, her weight was 98 kg (BMI = 37.8 kg/m^2) and blood pressure was 145/80 mmHg. She was keen to lose weight to improve her health and overall wellbeing, and wished to explore other options to aid with her efforts to lose weight.

Modest weight loss of 5–10% could result in significant clinical benefit and improvement of Sally's many obesity-related complications; unfortunately, the weight loss achieved with lifestyle modifications was not durable. Adjunctive therapies with pharmacotherapy or surgery would be appropriate considerations in this case.

Phentermine was considered but not chosen given her hypertension. Liraglutide was commenced, with a starting dose of 0.6 mg, and gradually escalated to 1.8 mg daily. Sally was unable to tolerate higher doses because of gastrointestinal side effects. The medication improved her adherence to caloric restriction, and she achieved weight loss of 5 kg.

Two years later, Sally's weight had increased to 108 kg (BMI = 41.7 kg/m^2). She discontinued liraglutide six months ago because of cost constraints. Sally expressed interest in bariatric surgery, and underwent an uneventful laparoscopic sleeve gastrectomy with no early surgical complications. Appropriate multivitamin, multimineral, calcium and vitamin D supplementation were prescribed.

Three months after surgery, Sally lost 20 kg (18.5% of her body weight). Her antihypertensive medications were decreased, and her blood pressure was 124/76 mmHg on perindopril 4 mg daily. Nutritional screening did not reveal any micronutrient deficiencies, and Sally was counselled on the importance of adherence to long-term postoperative follow-up to ensure a safe and successful outcome.

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