Glucagon-like peptide-1 receptor agonists for weight loss: Consider the case for selective pharmacotherapy

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OBESITY is a progressive, chronic and often relapsing disease that precipitates serious health consequences. More importantly, obesity reduces health-related quality of life for patients. Conventionally prescribed for treatment of diabetes, glucagon-like peptide-1 (GLP-1) receptor agonists (RAs) are also increasingly used in weight management as the prevalence of obesity rises.[1,2] According to the Australian Bureau of Statistics, 67% of adults were either overweight or obese in 2018, up from 63% in 2014.[3] Alongside supportive lifestyle counselling, and in the context of the high number of patients who undergo potentially unnecessary bariatric surgery, we highlight the rationale of selective GLP-1 RA pharmacotherapy for obesity and present recommendations from around the world.

Liraglutide and semaglutide are analogues of the incretin hormone GLP with 97% homology to human GLP-1.[4] GLP activates GLP-1 receptors in the pancreas and central nervous system to enhance postprandial insulin release in a glucose-dependent manner, reduces glucagon secretion, delays gastric emptying and induces weight loss through decreased appetite and reduced energy intake.[5] Both liraglutide and semaglutide are given subcutaneously; liraglutide is administered once daily, whereas semaglutide is administered once weekly.[1,6] Currently, indications for obesity are Therapeutic Goods Administration approved but not subsidised on the Pharmaceutical Benefits Scheme (PBS). For patients eligible due to diabetes, only 1 mg semaglutide is available in Australia on the PBS, but 2.4 mg is available off-label as Wegovy® (semaglutide; Novo Nordisk , Bagsværd, Denmark). Worldwide guidelines addressing the use of pharmacotherapy for weight management are presented in Table 1.

Landmark randomised clinical trials examining the efficacy of GLP-1 RAs as an adjunct for weight management are presented in Table 2. These studies found that a regimen of 3.0 mg liraglutide once daily resulted in an absolute reduction of mean body weight of 4.2–5.6 kg over 56 weeks compared with the placebo of lifestyle therapy only.[1,4,5] Similarly, 2.4 mg semaglutide weekly as an adjunct to lifestyle intervention resulted in losses ranging between 12.7 and 17.7 kg after 68 weeks.[2,6] Patients treated with liraglutide also showed concurrent reductions in cardiometabolic risk factors, with a decrease in total cholesterol by 2.3% and a decrease in systolic blood pressure of 2.8 mmHg.[1] Semaglutide improved the relative percentage of total cholesterol by 7.1% and systolic blood pressure by 2.7 mmHg.[6] Evidence for cardiovascular risk reduction is a strong clinical consideration for the use of GLP-1 RAs in conjunction with a healthy low-calorie diet. There is also evidence showing some loss of muscle mass with GLP-1 RAs,[2] which should be maintained with ongoing exercise. Weight regain is commonly seen after cessation, demonstrating the value of sustained pharmacotherapy when significant lifestyle changes are not established.[4] In the SCALE trial, those in the liraglutide or semaglutide groups reported higher 'impact of weight on quality of life' scores across all domains of physical function, self-esteem, sexual life, public distress and work.[4] Caution is advised if patients wish to cease medication, and to consider long-term use in high-risk patients for which there are safety data.[2,4]

Common adverse effects of GLP-1 RAs are gastrointestinal events that include

Table 1. Summary of guidelines for the use of pharmacotherapy for obesity

Guideline	Year	Recommendation
NICE[7]	2020	• Liraglutide is recommended as an option for managing overweight and obesity alongside a reduced-calorie diet and increased physical activity in adults only if: – they have a BMI of at least 35 kg/m^2 – they have non-diabetic hyperglycaemia – they have a high risk of cardiovascular disease – it is prescribed in secondary care by a specialist multidisciplinary weight management service – the company provides it according to the commercial arrangement.
AACE/ACE[8]	2016	• Pharmacotherapy for overweight and obesity should be used only as an adjunct to lifestyle therapy and not alone. • Pharmacotherapy should be offered to patients with obesity, when potential benefits outweigh the risks, for the chronic treatment of their disease. Short-term treatment (3–6 months) using weight loss medications has not been demonstrated to produce longer-term health benefits and cannot be generally recommended based on scientific evidence.
ADS[3]	2016	• Weight loss pharmacotherapy might be useful in assisting with the initial weight loss, to maintain weight loss at the end of a VLED or to prevent weight regain. Although weight loss pharmacotherapy will usually be required on a long-term basis, data on long-term safety and effectiveness of weight loss medication are limited. Only three drugs have been approved by the TGA for the treatment of obesity in Australia: phentermine, orlistat and liraglutide. • Supervised lifestyle intervention is the mainstay of management for individuals with a BMI 30–40 kg/m^2 without established complications. Initially this includes a RED or an LED, combined with a program to increase regular physical activity. Referral to multidisciplinary care, such as an accredited practising dietitian, exercise physiologist, lifestyle coach or an established commercial weight loss program, can be considered. If weight loss is insufficient or weight regain is experienced, a VLED can be considered or a RED/LED can be combined with pharmacotherapy. • Individuals with a BMI 30–40 kg/m^2 with obesity-related complications or a BMI >40 kg/m^2 without complications require more intensive interventions. Three main options are available and the choice of therapies should be guided by previous weight loss interventions and response: – VLED is an initial option for individuals who have not tried this previously and are willing to use meal replacements – Pharmacotherapy can be considered in individuals who do not have an adequate initial response to the VLED, or who regain weight once the VLED is relaxed – Bariatric surgery is an option for individuals who do not respond to the VLED plus pharmacotherapy, or who have previously tried this approach without success, or who have T2D.
Obesity Management Task Force of the EASO[9]	2015	• Pharmacological treatment should be considered as part of a comprehensive strategy of disease management. Pharmacotherapy can help patients maintain compliance, ameliorate obesity-related health risks and improve quality of life. It can also help prevent the development of obesity comorbidities (eg T2D). • Current drug therapy is recommended for patients with a BMI ≥30 kg/m^2 or a BMI ≥27 kg/m^2 with an obesity-related disease (eg hypertension, T2D, sleep apnoea). • The efficacy of pharmacotherapy should be evaluated after the first 3 months. If weight loss achieved is satisfactory (>5% weight loss in non-diabetic and >3% in diabetic patients), treatment should be continued. Treatment should be discontinued in non-responders.

AACE, American Association of Clinical Endocrinologists; ACE, American College of Endocrinology; ADS, Australian Diabetes Society; BMI, body mass index; EASO, European Association for the Study of Obesity; LED, low-energy diet; NICE, National Institute for Heath and Care Excellence; RED, reduced-energy diet; T2D, type 2 diabetes; TGA, Therapeutic Goods Administration; VLED, very low-energy diet.

Table 2. Efficacy of trials for glucagon-like peptide receptor agonists as an adjunct in weight management

Trial	Year	Country/sites of study	No. enrolled	Study duration (weeks)	GLP-1 RA	Mean BMI of participants (kg/m²)	Mean change in BMI vs placebo (kg/m²)	Mean change in body weight vs placebo (kg)
Weghuber et al[6]	2022	Austria, Belgium, Croatia, Ireland, Mexico, Russia, UK, US	201	68	Semaglutide 2.4 mg	37.0	−6.0	−17.7 (−17.4%)
Wilding et al[2]	2021	Asia, Europe, North America, South America	1961	68	Semaglutide 2.4 mg	37.9	−4.61	−12.7 (−12.44%)
Kelly et al[5]	2020	Belgium, Mexico, Russia, Sweden, US	251	56	Liraglutide 3.0 mg	35.5	−1.58	−4.5 (−5.01%)
Pi-Sunyer et al[1]	2015	Europe, North America, South America, Asia, Africa, Australia	3731	56	Liraglutide 3.0 mg	38.3	−2.0	−5.6 (−5.4%)
Davies et al[4]	2015	France, Germany, Israel, South Africa, Spain, Sweden, Turkey, UK, US	846	56	Liraglutide 3.0 mg	37.2	−1.5	−7.1 (−6.7%)

BMI, body mass index; GLP-1 RA, glucagon-like peptide-1 receptor agonist.

nausea, vomiting and diarrhoea or constipation. These mostly occur during dose escalation and become less frequent over time.[5] One trial found that 92.9% of patients treated with liraglutide experienced one or more adverse events, but such incidents were high at 85.8% even for those in the placebo group.[4] Similarly, in another trial, 89.7% of patients in the semaglutide group reported adverse events, compared with 86.4% in the placebo group.[2] Most adverse events have been reported as mild in severity across all studies.[1,2,5,6] Transient nausea and vomiting during treatment with liraglutide stimulated even greater weight loss when these symptoms were tolerable, and did not appear to attenuate quality of life improvements.[10] Other adverse effects include gallbladder issues, where slightly higher rates of cholelithiasis and cholecystitis were reported by those treated with liraglutide (2.5% vs 1.0%) or semaglutide (2.6% vs 1.2%) compared with placebo.[1,2] Hypoglycaemic events were rare and none were deemed serious in severity.[5,6] GLP-1 RAs can also infrequently cause pancreatitis, at a rate of approximately 3.4 per 1000.[1,2] There is no definitive evidence on increased risk of thyroid cancer in humans, but it might be a clinical consideration when prescribing to patients with specific risk factors.[1,6] Of the several reported deaths during these trials, none were associated with GLP-1 RAs after independent blinded adjudication.[1,4]

As general practitioners, it is important that we educate patients and other health providers about the importance of positive lifestyle interventions. It is also important to be aware of current recommendations for pharmacotherapy as an adjunct to conventional weight loss strategies. Resources such as The Australian Obesity Management Algorithm[3] provide useful up-to-date information for general practitioners on when and how to initiate pharmacotherapy. Both current and new medications such as tirzepatide, a dual glucose-dependent insulinotropic peptide (GIP) RA and GLP-1 RA, will likely continue to be increasingly prescribed in Australia. Other existing therapies, such as orlistat, can also be prescribed, although they are likely to be less efficacious as observed in randomised trials involving obese non-diabetic adults.[10] Treatment with GLP-1 RAs should be considered alongside a healthy low-calorie diet and exercise to maximise efficacy and deliver best practice care to patients around Australia.

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