ARTICLE

Injectable drugs for weight management

SUMMARY

Obesity management is complex; medications must be used in conjunction with behavioural changes and monitoring by health professionals.

Injectable drugs for weight management include glucagon-like peptide-1 (GLP-1) receptor agonists (e.g. liraglutide, semaglutide) and dual glucose-dependent insulinotropic polypeptide (GIP)/GLP-1 receptor agonists (e.g. tirzepatide). These drugs contribute to weight loss by mimicking the incretin hormones GLP-1 and GIP to reduce appetite, change food enjoyment, slow stomach emptying and stimulate insulin release.

Regaining weight is common when these drugs are stopped, so they usually need to be continued long term.

Relatively minor gastrointestinal issues are common. There is also a small but real risk of more serious adverse effects, including gallstones and pancreatitis. It is important to monitor mental health, as these drugs can change a patient's relationship with food, and they may be misused by those without obesity.

Natasha Yates
General Practice Lead[1]
General Practitioner[2]

Terri-Lynne South
General Practitioner and Medical Director[3]

[1] New Medical Education Australia, Brisbane
[2] Medical on Robina, Gold Coast, Queensland
[3] Lifestyle Metabolic, Brisbane

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Introduction

Injectable glucagon-like peptide-1 (GLP-1) receptor agonists (e.g. liraglutide, semaglutide) and dual glucose-dependent insulinotropic polypeptide* (GIP)/GLP-1 receptor agonists (e.g. tirzepatide) are increasingly used for weight loss and weight maintenance (weight management) for people who are overweight or living with obesity. Their efficacy and the high prevalence of overweight and obesity have led to wide and growing use in Australia. However, obesity is multifactorial and complicated, and prescribing injectables is only one aspect of effective management.

Prescribers need to be aware of how injectables for weight management work, to incorporate them into safe and evidence-based management. This includes understanding the variability between different products in dosing, devices, efficacy and costs; recognising that patients may have unrealistic expectations and aligning these with realistic outcomes; and monitoring for safety and adverse effects.

Obesity management is not only about achieving weight loss. Management of overweight and obesity should focus on fostering health improvements across the full biopsychosocial spectrum of an individual.[1] Injectable weight-loss drugs should be used as an adjunct to behavioural interventions. In clinical trials for these drugs, all participants received advice about behavioural and lifestyle modifications.[2-4] By aiding appetite regulation and reducing cravings, these drugs help patients adhere to behavioural changes more effectively.[5]

Many individuals living with obesity experience micronutrient deficiencies, disordered eating behaviours, and sarcopenia,[6,7] all of which can be worsened by weight loss. Prescribers must conduct thorough initial assessment, monitor regularly, and be able to coordinate support for patients, ideally with a multidisciplinary team. An individualised, integrated approach ensures that obesity management prioritises long-term health and overall wellbeing.[8]

Mechanisms of action

Injectable drugs to manage weight work by mimicking the incretin hormones GLP-1 and GIP. They act either at the GLP-1 receptor alone (liraglutide, semaglutide) or at both GLP-1 and GIP receptors (tirzepatide). In the brain this affects appetite centres, specifically the hypothalamus and mesolimbic pathway. The effect is to increase satiety, as well as reduce or change enjoyment of food. In the gut, movement of food is slowed, resulting in a prolonged feeling of fullness. The drugs also act on the pancreas, stimulating insulin production and reducing glucagon, which is why they were first developed for use in diabetes. These combined effects result in weight loss.

* Also known as gastric inhibitory peptide (GIP)

Approved indications

In Australia, GLP-1 and dual GIP/GLP-1 agonists are approved for chronic weight management as an adjunct to a reduced-energy diet and increased physical activity, in:

- adults with obesity (BMI greater than or equal to 30 kg/m^2)
- adolescents with obesity (weight greater than 60 kg and BMI on or greater than 95th percentile on sex- and age-specific BMI growth charts) (semaglutide only)
- adults who are overweight (BMI 27 to less than 30 kg/m^2) with at least one weight-related comorbidity.

As well as benefits for weight loss, these drugs have been shown to be effective in management of diabetes, secondary reduction of cardiovascular disease,[9,10] obstructive sleep apnoea, knee arthritis and kidney disease.[11] At the time of writing, the Therapeutic Goods Administration–approved indications, in addition to weight management, are:

- semaglutide (Wegovy only): reduction of cardiovascular risk in adults with established cardiovascular disease, BMI greater than or equal to 27 kg/m^2, and without diabetes
- tirzepatide: treatment of type 2 diabetes, and moderate to severe obstructive sleep apnoea in adults with overweight or obesity.

Note that semaglutide (Ozempic) does not have approval for weight management but is approved for type 2 diabetes and to reduce the risk of kidney function decline in adults with type 2 diabetes (Table 1).

Patient selection

Evaluating the clinical appropriateness for individual patients is imperative when prescribing injectable drugs for weight management. Details of clinical assessment are beyond the scope of this article and are well described elsewhere (see Further reading).

Failure to adequately assess and manage patients can result in harm; for example, failing to recognise the presence of an eating disorder, and inappropriately prescribing medication that enables a patient to persist with dangerous eating habits rather than offering appropriate and evidence-based care.[12,13]

Differences between injectable drugs for weight management

Significant differences between the various injectable drugs for weight management are the dosing schedule (Table 1) and efficacy in terms of weight loss (Table 2).

Safety and adverse effects

Between 6%[15] and 13.5%[16] of participants stopped taking the GLP-1 or GIP/GLP-1 agonist in clinical trials, primarily because of adverse effects on the gastrointestinal tract, biliary tract, eyes and mental health.

Gastrointestinal adverse effects are common with these drugs,[4] and include nausea, bloating, constipation and diarrhoea.[17] In rare cases, complete gastroparesis has been reported.[18]

Because of the slower transit of food through the stomach, the fasting period before surgery may not be sufficient to empty the stomach, potentially

Table 1 Injectable drugs for weight management

Drug name	Class	Approved indications [NB1]	Dose frequency
Liraglutide	GLP-1 receptor agonist	Weight management	Daily
Semaglutide	GLP-1 receptor agonist	Type 2 diabetes [NB2] Decline in kidney function with type 2 diabetes and chronic kidney disease [NB2] Weight management [NB3] Secondary cardiovascular disease risk management with BMI greater or equal to 27 [NB3]	Weekly
Tirzepatide	Dual GIP/GLP-1 receptor agonists	Weight management Type 2 diabetes Obstructive sleep apnoea	Weekly

BMI = body mass index; GIP = glucose-dependent insulinotropic polypeptide; GLP-1 = glucagon-like peptide-1

NB1: Approved indications are for adults, with the exception of semaglutide (Wegovy) which is approved for weight management in adults and adolescents.

NB2: Approved indications are for semaglutide (Ozempic) only.

NB3: Approved indications are for semaglutide (Wegovy) only.

Table 2 Comparative weight loss with injectable obesity drugs

Drug, comparator and trial name	Mean weight loss		Percentage weight loss				Trial details
	%	kg	≥5%	≥10%	≥15%	≥20%	
Liraglutide 3.0 mg daily versus placebo (SCALE)[3]	8.0% versus 2.6%	8.4 kg versus 2.8 kg	63.2% versus 27.1%	33.1% versus 10.6%	14.4% versus 3.5%	–	• 56 weeks • randomised double-blind • plus 'counselling on lifestyle modification'
Semaglutide 2.4 mg weekly versus placebo (STEP 1)[2]	14.9% versus 2.4%	15.3 kg versus 2.6 kg	86.4% versus 31.5%	69.1% versus 12.0%	50.5% versus 4.9%	32.0% versus 1.7%	• 68 weeks • randomised double-blind, placebo-controlled • plus 'lifestyle interventions'
Tirzepatide 5 mg weekly versus placebo (SURMOUNT-1)[4]	15.0% versus 3.1%	16.1 kg versus 2.4 kg	85% versus 35%	–	–	–	• 72 weeks • phase 3 double-blind, randomised controlled • plus 'lifestyle interventions'
Tirzepatide 10 mg weekly versus placebo (SURMOUNT-1)[4]	19.5% versus 3.1%	–	89% versus 35%	–	–	50% versus 3%	
Tirzepatide 15 mg weekly versus placebo (SURMOUNT-1)[4]	20.9% versus 3.1%	23.6 kg versus 2.4 kg	91% versus 35%	–	–	57% versus 3%	
Tirzepatide 10 to 15 mg weekly versus semaglutide 1.7 to 2.4 mg weekly (SURMOUNT-5)[14]	20.2% versus 13.7%	22.8 kg versus 15.0 kg	–	81.6% versus 60.5%	64.6% versus 40.1%	48.4% versus 27.3%	• 72 weeks • phase 3b open-label, randomised controlled

increasing risk for patients receiving general anaesthesia or deep sedation.[19] A clear fluid diet is recommended for 24 hours in addition to standard 6-hour fasting prior to procedures requiring general anaesthesia.[20]

GLP-1 agonists and dual GIP/GLP-1 agonists may increase risk of pancreatitis and gallstones.[15] Concerns have also been raised around the risk of thyroid and pancreatic cancers, although current research is reassuring.[21,22] However, these types of cancers are rare, so it is unlikely we will know if there is any 'small-but-significant' increase for some years to come.[23]

Worsening of diabetic retinopathy has been reported in association with GLP-1 use.[9,24] However, this has not been a consistent finding, and subsequent studies have not shown harmful retinal effects in those without diabetes.[25]

An association between nonarteritic anterior ischaemic optic neuropathy (NAOIN) and GLP-1 agonists has been observed; further study is needed to confirm or exclude causality.[26]

GLP-1 and dual GIP/GLP-1 agonists may also impact mental health.[5] Prescribers should discuss and monitor mental health, and provide appropriate support, interventions and referrals as needed.

Important mental health safety issues include:

- **The impact on patients' relationship with food and pleasure**: The fact these drugs often interfere with the pleasure of eating makes assessment and investigation of appetite loss potentially complicated, as other serious illnesses, including infection, cancer, depression, or an eating disorder, could be missed. Additionally, the loss of pleasure in food may have psychosocial impacts that exacerbate mental health conditions like depression, suicidal ideation and suicidal action – this is a current area of active research.[5,27]
- **The potential for injectables to be used by people who do not have, or no longer have, obesity, particularly those with eating disorders**: Appetite suppression induced by these drugs may lead to self-starving or poor nutritional intake. The psychological and social pressure to be thin is a powerful driver for some people, particularly in a society that frequently stigmatises obesity. Prescribers need to be able to manage requests for weight-loss drugs from people who do not have obesity, in a way that addresses their reasons for requesting them. Asking 'What has been your highest weight?' may give helpful insight into patients' histories and mindsets.[28]

- **The potential impact on mental health for those who do not respond to the drugs:** There is no published research around this. In the original semaglutide randomised controlled trial, which showed significant weight loss for most participants, 14% of participants failed to lose even 5% of their body weight, after taking the drug for more than 1 year.[2]

Administration

Injectable GLP-1 and dual GIP/GLP-1 agonists are available as pen devices and administered subcutaneously. Some have needles provided in the box and others require needles to be purchased separately.

Each new pen of liraglutide and semaglutide needs to be primed once before first use. Priming prior to each dose is recommended with tirzepatide. Instructions are included in leaflets provided with each product.

Storage

When not in active use, pens need to be stored in a refrigerator. When in use, pens can be stored at room temperature (around 20°C) for 4 to 6 weeks. They should be kept away from direct light (cap on) and extreme temperatures.

How to prescribe injectable drugs for weight loss

Prescribing weight management drugs requires a thorough harm–benefit analysis, informed patient consent, addressing both known and potential adverse effects, as well as setting realistic expectations for outcomes including the potentially long-term nature of treatment.

The initial dose is intentionally subtherapeutic, to minimise adverse effects. This is followed by incremental increases to achieve the required clinical response, which may occur at a dose lower than the amount recommended by the manufacturer. See Box 1 for practical tips around prescribing.

At the time of writing, none of these drugs are listed on the Pharmaceutical Benefits Scheme (PBS) for weight management. They are PBS-subsidised for management of type 2 diabetes only. Therefore, costs to the patient vary but can be up to hundreds of dollars per month. Some private health policies will provide patients with a partial rebate. Affordability and access are therefore substantial barriers for many people, potentially exacerbating existing health inequities.

Weight regain after stopping treatment

Obesity is not cured by GLP-1 or dual GIP/GLP-1 agonists. For most patients being treated with these drugs, maintaining weight reduction requires long-term use, along with multidisciplinary input and sustained behavioural and lifestyle modification. When treatment is stopped, regaining weight is the norm.

The STEP 1 trial (68 weeks of semaglutide versus placebo *plus* lifestyle intervention for both groups) was extended for 12 months to assess weight regain after stopping treatment. Twelve months after stopping, the proportion of participants with weight loss of 5% or more fell from 86.4% to 48.2% in the semaglutide group and 31.5% to 22.6% in the placebo group.[29]

A systematic review preprint (available but not yet peer reviewed), reporting on weight gain after stopping GLP-1 agonists, estimated weight regain plateaus at around 75% of the weight lost on treatment.[30] Of particular concern is that weight may be regained proportionally more as fat and not muscle, which carries additional health risks.[31] Patients should be supported to build and maintain muscle while on treatment and once they have stopped.[32]

Reasons to stop treatment

There are a number of reasons someone may stop treatment:

- **Adverse effects**: If these are predominantly mild and gastrointestinal tract–related, dose reduction can be considered rather than stopping treatment. For more severe or irreversible adverse effects (e.g. pancreatitis, gastric paresis, adverse mental health effects), stopping immediately is recommended.

Box 1 Practical tips for prescribing injectable drugs for weight management

- Start at the lowest dose and slowly increase at the recommended intervals as tolerated.
- Individualise the dose based on the patient's response (efficacy) and tolerance (adverse effects).
- If the patient has intolerable adverse effects, reduce the dose or remain at the current dose for a longer period until the adverse effects subside.
- Provide advice to the patient to reduce the risk of potential adverse effects, such as recommending smaller meals, avoidance of heavy, high-fat meals, and good hydration to limit nausea.
- Be familiar with the range of products available, some of which are fixed-dose devices (offering some safety advantages) and some of which have variable dosing (offering dose flexibility from the same device).
- Consider cost to the patient, as this is a major factor influencing accessibility and long-term adherence.

- **Lack of efficacy**: Clinical trial nonresponse rates for injectable obesity drugs were 10 to 15%, with higher nonresponse rates seen in patients with type 2 diabetes.[33] There may be a combination of reasons for this including genetics, gender, behaviour and lifestyle habits, mental health, medication adherence or tolerance, and psychosocial drivers of eating.[33]
- **Pregnancy**: Patients should be advised to stop before pregnancy; 1 month prior for liraglutide, and 2 months prior for semaglutide and tirzepatide.[34,35]

Conclusion

Injectable GLP-1 agonists and dual GIP/GLP-1 agonists are effective in facilitating weight loss and weight maintenance through appetite regulation and metabolic effects but are not a standalone solution. Obesity is a chronic, multifactorial condition and use of injectable weight-management drugs must be integrated into holistic, multidisciplinary care that prioritises overall health improvements for the individual.

Long-term use of these drugs is generally required for sustained weight reduction, alongside ongoing behavioural and lifestyle interventions, and supportive care to maintain muscle mass. There is a significant issue of weight regain when these drugs are stopped. ≺

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