



GLP-1 RECEPTOR AGONISTS IN OBESITY MANAGEMENT: EFFICACY, TOLERABILITY AND SUPPLY CHALLENGES

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1. INTRODUCTION

Obesity is now a global condition in the plainest sense. Pooled analyses of national surveys show that the number of adults with a body mass index (BMI) in the obese range rose several-fold between 1975 and 2016, in rich and poor countries alike [1]. For most of that period drug treatment played a small part. Older anti-obesity medicines gave modest weight loss, often carried troublesome adverse effects and were withdrawn or restricted, so clinicians relied mainly on lifestyle advice and, for the most severe cases, bariatric surgery [2, 3, 4]. Expectations were

Abstract

Glucagon-like peptide-1 (GLP-1) receptor agonists have moved from diabetes clinics into everyday obesity care, and demand now exceeds what manufacturers and health systems can easily supply. This mini review summarises published trial and safety literature on liraglutide, semaglutide and the dual agonist tirzepatide in adults and adolescents with obesity. It covers pharmacology, weight-loss efficacy, maintenance after stopping, cardiometabolic benefit, gastrointestinal and other adverse effects, and the supply, cost and access problems that follow from rapid uptake. The review reports no new data. The evidence shows large average weight loss with tolerable but frequent side effects, while long-term outcomes, equitable access and supply security remain unresolved.

low and, to be fair, so were results. Population growth does not explain it. Rises in prevalence were steepest in low- and middle-income regions after the turn of the

century, which means that health systems with the fewest resources are now facing the largest numbers of patients who might ask for these products.

That picture has changed within a few years. Peptides based on glucagon-like peptide-1 (GLP-1), first developed for type 2 diabetes, produced weight loss in diabetic patients that was larger than anyone had designed for, and dedicated obesity trials followed [5, 6, 7]. Average losses of 10 to 20 per cent of body weight are now reported with the newer agents, figures that had been seen before only after surgery [7, 8]. Prescriptions have risen sharply, public interest has grown even faster, and pharmacists have found themselves answering questions about injection technique, nausea and why the product is out of stock. That enthusiasm should be tempered by memory. Earlier obesity drugs also arrived with large claims and left under a cloud of safety concerns, so the current wave of evidence deserves scrutiny from people who will actually be dispensing the products and answering patients' questions about them.

This mini review brings together the published evidence on GLP-1 receptor agonists in obesity, with attention to three questions that matter in practice. How much do they achieve, and for whom? What do patients put up with in return? And can supply chains and payers actually deliver them to the people who might benefit? It draws on randomised trials, regulatory documents, narrative reviews and safety analyses, and it reports no new data. Findings are described as reported by the original authors, and numbers are quoted only where they are widely cited and consistent across sources. The sections that follow move from pharmacology through efficacy, durability and safety to supply and access, and close with practical implications for pharmacists and a short account of what the evidence cannot yet tell us. Table 1 and fig. 1 are cited in the efficacy section, where the main trial results are collected.

2. PHARMACOLOGY AND AVAILABLE AGENTS

Native GLP-1 is released from intestinal L-cells after meals. It enhances glucose-dependent insulin secretion,

suppresses glucagon, slows gastric emptying and acts on hypothalamic and brainstem circuits that reduce appetite and food reward [9, 10, 11]. The natural hormone is also fleeting, with a circulating half-life of only a couple of minutes because dipeptidyl peptidase-4 (DPP-4) cleaves it almost at once and the kidney clears the remainder [10]. A therapeutic version must therefore resist that enzyme and linger in the circulation, and most of the medicinal chemistry in this field has been spent on exactly those two problems. The receptor itself is widely distributed, with expression in pancreatic islets, the stomach, the heart, the kidney and several brain regions, which helps to explain why a single class of drugs produces glycaemic, gastrointestinal, cardiovascular and appetite effects together [9, 11]. The anorectic action appears to depend mainly on central receptors, although peripheral vagal signalling contributes.

Liraglutide solved the problem with a fatty acid side chain that promotes albumin binding and self-association at the injection site, giving a half-life of about thirteen hours and daily dosing [5]. Semaglutide went further. An amino acid substitution protects the peptide from peptidase attack, and a longer diacid chain with a spacer binds albumin more tightly, which extends the half-life to roughly a week and permits weekly injection [12, 13]. An oral formulation of semaglutide uses an absorption enhancer in the stomach and has also been tested at higher doses for weight loss [14]. Exposure to semaglutide is largely independent of injection site, and elimination occurs through proteolytic degradation and excretion of metabolites in urine and faeces, with no single organ dominating, which is why dose adjustment for renal or hepatic impairment is usually not needed [13]. The long half-life has a flip side, however. Adverse effects that begin after a dose increase can persist for days, and stopping the drug does not bring immediate relief.

Tirzepatide adds a second target. It is a single peptide that activates both the glucose-dependent insulinotropic polypeptide (GIP) receptor and the GLP-1 receptor, with a fatty diacid moiety that prolongs its action,

and in cell studies it is imbalanced, favouring the GIP receptor over the GLP-1 receptor [15]. Why co-activation of GIP should add to weight loss is still argued, since GIP has opposite effects in some experimental settings, and the proposed explanations include better tolerability of the combined signal and direct central effects [11, 15]. What matters for the clinic is that the dual agonist gave larger glucose and weight reductions than a pure GLP-1 agonist in head-to-head testing in diabetes, as reviewed elsewhere [16]. Earlier work in animals suggested that receptor-level differences between the two hormones could explain the added effect, with GIP possibly reducing nausea at central sites, but the human evidence on mechanism is still thin and some of the interpretations remain speculative [15, 16]. Further agents that add glucagon-receptor activity or amylin analogues are being studied, though none belongs in this review's evidence base.

Table 1: Published weight-loss results for GLP-1 based agents in randomised trials

Agent / trial setting	Reported finding	Ref.
Liraglutide 3.0 mg daily adults with prediabetes	Modest average loss sustained over three years, clearly above placebo.	[6]
Liraglutide vs semaglutide head-to-head, diabetes	Semaglutide gave markedly larger average weight loss than liraglutide.	[17]
Semaglutide 2.4 mg weekly East Asian adults	Mean loss near 13% at 68 weeks, clearly above placebo.	[7]
Semaglutide 1 mg weekly type 2 diabetes	Weight fell alongside glycaemic gains, by less than in adults without diabetes.	[18]
Liraglutide plus behavioural therapy intensive programme	Greater loss than placebo with the same structured counselling, but smaller than newer agents.	[19]
Weight maintenance after diet liraglutide	Liraglutide gave further loss after a low-calorie diet; placebo gave almost none.	[20]
Oral semaglutide 50 mg daily adults with obesity	Loss similar to weekly injection; fasting administration required.	[14]
Semaglutide in adolescents weekly injection	Large reduction in body mass index relative to placebo.	[21]

Agent / trial setting	Reported finding	Ref.
Tirzepatide weekly Chinese adults, no diabetes	Dose-related mean loss of roughly 14 to 18% at 52 weeks.	[8]
Tirzepatide weekly type 2 diabetes	Weight fell by roughly 7 to 13 kg over a year, whereas insulin comparator gained weight.	[22]
Body composition weight loss from restriction	Fat-free mass makes up a meaningful minority of the weight lost, supporting protein and exercise.	[23]

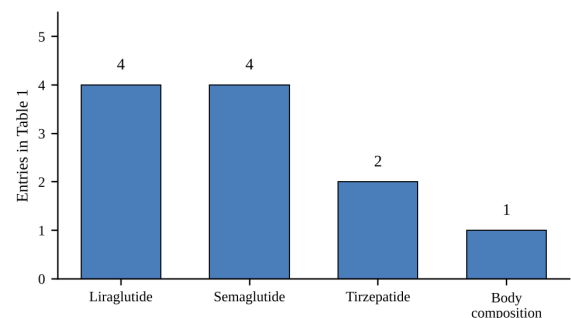


Fig. 1: Number of entries in table 1 by agent

3. CLINICAL EFFICACY IN OBESITY

The efficacy case begins with liraglutide 3.0 mg, which in a three-year trial of people with prediabetes and overweight or obesity produced mean weight loss of about six per cent, against roughly two per cent with placebo [6]. That result was real but modest. A larger step came with weekly semaglutide 2.4 mg, where average loss at 68 weeks in an East Asian population was about 13 per cent of body weight compared with about 2 per cent for placebo, both groups receiving lifestyle counselling [7]. Many treated participants lost a tenth or more of their weight. These absolute figures should be read alongside the control arms, because participants given placebo plus lifestyle advice still lost a little weight, and because trial volunteers tend to be more motivated than the general population. Reporting as a percentage of baseline weight also hides that a person who starts at 130 kg loses far more in kilograms than one starting at 95 kg.

Results are smaller in type 2 diabetes, a pattern seen with almost every weight-loss intervention. In patients with type 2 diabetes given semaglutide at the lower 1 mg dose, weight fell alongside glycaemic control, by

clearly less than in adults without diabetes who were treated for obesity [18]. Adding intensive behavioural therapy to liraglutide gave a clear advantage over placebo with the same counselling, though absolute losses stayed smaller than with the newer agents [19]. For tirzepatide, mean loss in Chinese adults without diabetes was roughly 14 to 18 per cent over 52 weeks across the doses studied [8], and in people with type 2 diabetes weight fell by a smaller amount, roughly 7 to 13 kg over a year across the doses studied [22]. Some of the difference between groups with and without diabetes is explained by insulin resistance and by concurrent glucose-lowering drugs that promote weight gain, such as insulin and sulfonylureas, which blunt the effect of the incretin drug [18, 22]. Doses in diabetes trials were also generally lower than those used for weight management.

Direct comparisons are few, so cross-trial judgements need care. A randomised comparison of semaglutide 1 mg with liraglutide 1.2 mg in adults with type 2 diabetes found markedly greater weight loss with semaglutide, roughly three times as much [17]. Tirzepatide was compared with semaglutide 1 mg in diabetes, where it gave larger reductions in both HbA1c and body weight [16]. Differences in dose, population and trial design rule out simple league tables. The main published efficacy results are brought together in table 1 and their distribution by agent and setting is shown in fig. 1. Another reason for caution is that the tirzepatide and semaglutide trials were run in different years under different supply, recruitment and background conditions, and the active comparator in diabetes was a lower semaglutide dose than the one now used for obesity [7, 16]. Head-to-head trials at the highest licensed doses in people with obesity are still few, so such comparisons remain provisional.

An oral route has now been tested seriously. Semaglutide taken as a 50 mg daily tablet produced mean loss near 15 per cent at 68 weeks in adults with overweight or obesity, similar in magnitude to the weekly injection, although tablets require fasting administration with a small volume of water and strict

spacing from food [14]. Adolescents have also been studied. Weekly semaglutide in teenagers with obesity gave a large reduction in BMI relative to placebo over 68 weeks, which prompted regulators and guideline groups to reconsider the lower age limits for pharmacotherapy [21]. Both oral and adolescent data are limited by trial length, and access to the tablet at doses used in the trial depends on regulatory decisions that differ between countries [14, 21]. Adherence to the strict fasting rules is a practical concern for pharmacists.

4. WEIGHT MAINTENANCE AND BENEFITS BEYOND WEIGHT

Chronic disease needs chronic treatment, and the trial data on stopping make that point bluntly. Weight loss meets a strong biological defence: in a classic study, hormonal changes that favour regain, including lower leptin and peptide YY and higher ghrelin and hunger, were still present a year after diet-induced loss [24]. A randomised maintenance trial showed the practical side: after a low-calorie diet, people given liraglutide kept the loss and lost more, while those on placebo lost almost nothing further [20]. Tirzepatide follows a similar course, with losses accumulating over the first year before levelling off [8]. It is also worth recalling how the weight-loss curve behaves. Loss usually plateaus after about a year of treatment, so a falling curve followed by a flat line is expected, and a patient who stops losing at that point has not necessarily failed the drug [7, 8]. Counselling at the plateau helps prevent premature discontinuation.

This shapes how the drugs should be framed to patients. They are not a course of treatment with an end date like an antibiotic, and prescribers who describe them as a short-term fix are setting up disappointment. The more realistic comparison is with antihypertensives or statins, taken long term to hold a gain. That framing carries its own difficulty, because indefinite treatment multiplies the cost and the supply burden, and because data beyond a few years of continuous use remain limited [4, 20, 24]. Even so, many patients and doctors find it hard to accept. Obesity is still widely seen as a failure of willpower, and the idea that a medicine is needed indefinitely

clashes with that view. Pharmacists who understand the biology of weight regulation, including the hormonal drive to regain lost weight, can explain why the regain is expected and not a personal failing.

Cardiovascular outcomes are where the strongest long-term evidence lies. In patients with type 2 diabetes and high cardiovascular risk, liraglutide reduced major adverse cardiovascular events (MACE) relative to placebo in a dedicated outcome trial [25]. The SELECT trial was designed to test semaglutide 2.4 mg against placebo in adults with established cardiovascular disease and overweight or obesity but no diabetes, with major cardiovascular events as the primary outcome [26]. These results moved the discussion from cosmetic weight loss toward disease modification, and affected how payers read the economic case. The outcome trials also differ in participants. The earlier diabetes trials recruited people with established disease or high risk, and benefit might not extend to lower-risk groups, while the obesity outcome trial excluded diabetes and had a long follow-up, which makes it easier to apply to a population seeking treatment for weight alone [25, 26]. Mechanisms are not settled either, since the benefit appeared early in follow-up, before large weight loss had accumulated, which suggests effects beyond weight.

Other conditions have responded too. Semaglutide improved symptoms and exercise function in heart failure with preserved ejection fraction in people with obesity [27] and reduced knee pain in those with osteoarthritis [28], and tirzepatide lowered the frequency of breathing events in obstructive sleep apnoea [29]. Each of these studies was short or focused on symptoms rather than hard outcomes, so the results are best read as encouraging signals. Still, they hint that the drugs act on several obesity-related disorders at once, which complicates the question of who should be treated first. None of these trials was designed to show that weight loss itself explains the improvement, and all of them were funded by the manufacturers [27, 28, 29]. Independent confirmation, ideally including mortality and quality-of-life outcomes, would strengthen

the case, as would comparisons with usual care in routine settings.

5. TOLERABILITY AND SAFETY

Gastrointestinal effects dominate the adverse event profile. Nausea, vomiting, diarrhoea and constipation are the most commonly reported problems across the class, are dose related, and cluster in the escalation phase [30, 31]. In the East Asian semaglutide obesity trial gastrointestinal effects, mainly nausea and diarrhoea, were the most common adverse events, though most episodes were mild to moderate and short lived, and only a small minority stopped treatment because of them [7]. Tirzepatide shows a comparable pattern [8]. Slow titration, smaller meals, avoiding fatty food and stopping at the first sense of fullness are the standard advice from practice guidelines [32]. Practical steps reduce the burden. Splitting the dose escalation into longer intervals, taking the injection at a time that avoids social meals, and treating constipation early are all reasonable measures, even though few have been tested in randomised trials [16, 32]. Patients with a history of eating disorder, gastroparesis or inflammatory bowel disease deserve a more careful assessment before they start.

Rarer gastrointestinal and biliary events have received growing attention. A large cohort study in patients with diabetes found a higher risk of gallbladder and bile duct disease with GLP-1 receptor agonists, especially with longer use [33]. A population-based case-control study in people with type 2 diabetes reported higher odds of hospitalisation for acute pancreatitis among users of incretin-based therapy than among non-users [34]. By contrast, pooled trial data have not shown a clear excess of pancreatitis or pancreatic cancer, and the debate about causality continues [35, 36]. Case ascertainment in these studies is uneven. Pancreatitis and gallbladder disease are also more common in people with obesity and rapid weight loss for reasons that have nothing to do with the drug, so separating drug effect from background risk is difficult, and the conclusions of observational work depend heavily on the comparator chosen [33, 34, 36]. Rapid weight loss of any kind raises

the risk of gallstones.

Thyroid cancer was a concern from animal work, in which rodents given GLP-1 agonists developed C-cell hyperplasia and tumours through a receptor mechanism that is much less prominent in primates and humans [37]. Human evidence has not confirmed a risk, but the products carry a boxed warning and are contraindicated in people with a history of medullary thyroid carcinoma (MTC) or multiple endocrine neoplasia type 2 (MEN 2) [38]. Retinal complications deserve mention as well. Early diabetes trials hinted at worsening retinopathy with semaglutide, an effect analyses tied largely to the speed of glucose lowering [39], and an observational study linked semaglutide with non-arteritic anterior ischaemic optic neuropathy, an association still being tested [40]. Reports of eye problems should not lead patients to stop treatment unaided. Diabetic retinopathy screening should continue as usual, and sudden visual loss warrants urgent assessment, whatever its cause [40]. Absolute risks reported so far are low, and the studies cannot prove causation.

Other practical concerns affect pharmacy and perioperative care. Delayed gastric emptying means that food may remain in the stomach after a normal fasting period, and anaesthetic societies have published advice on whether to hold weekly doses before elective procedures. Oral contraceptive absorption might change with tirzepatide, so counselling on additional contraception is advised at initiation and dose increases [38]. Mood and suicidality have been examined because of earlier anti-obesity drugs, and regulators have so far found no causal signal, yet monitoring continues [4, 32]. Reports of dehydration and kidney injury follow vomiting, particularly in older patients [31]. Hypoglycaemia is uncommon with these drugs alone, but the risk rises when they are combined with insulin or sulfonylureas, so doses of those agents are often reduced at the start of treatment [31, 38]. Pharmacists reviewing a diabetic patient's regimen should look for this.

6. SUPPLY, COST AND ACCESS

Success has created a supply problem. Semaglutide and tirzepatide are complex

peptides made by recombinant or synthetic routes in specialised facilities, and the final products are filled into pen injectors, a step that has repeatedly limited output when demand outpaced forecasts [41]. Shortages of semaglutide and then of tirzepatide were declared by national regulators in recent years, leaving diabetic patients, who rely on these medicines for glucose control, competing with people seeking weight loss [41]. Expanding capacity takes years, so shortages are not quickly cured by purchasing alone. Cold-chain handling adds further fragility. The pens need refrigeration before first use, and logistics failures can spoil stock in hot climates, which matters in countries where electricity supply is uneven and where the prevalence of obesity is climbing [41]. Each of these links has to hold for the product to reach the patient in good condition.

Shortages tend to bring informal markets with them. Compounded copies of branded peptides, products sold online without prescription and counterfeit pens have all been reported, and pharmacists are often the first to see the harm, from dosing errors caused by unfamiliar vial concentrations to contaminated injections [41]. The pharmacist's role is to verify supply sources, to teach correct dose measurement, and to report suspect products. Patients should also know that a product that is cheaper than the licensed one may have no assurance of purity, sterility or even identity. Public warnings from regulators and professional bodies have urged people to buy only from licensed sources and to check pen labelling and packaging before use. Reports of overdose from incorrect syringe measurements show how small errors in unit conversion can cause severe vomiting and hospital admission, particularly in people drawing doses from multi-dose vials [38, 41].

Price is the second barrier. List prices of branded weekly injections in several countries are far above those of older oral drugs, and many health systems do not reimburse obesity treatment at all, or only for patients with a high body mass index plus comorbidity [4, 32, 41]. Modelling studies disagree about cost-effectiveness because they assume different durations of treatment

and different rates of weight regain. Equity is a worry, since the people with the highest burden of obesity are often those with the least ability to pay. Questions of prioritisation therefore sit alongside questions of supply. Some payers cover the drugs only when patients meet ongoing criteria, such as achieving a set percentage of weight loss within a given period, which in effect stops treatment for those who respond slowly. Such rules may save money but create a risk that the people for whom the medicines help most are cut off at the moment of benefit [4, 24].

Priority rules are one response. Some professional bodies have suggested that, during shortages, supply should be protected for patients with type 2 diabetes before starting new patients on obesity treatment, and that prescribers should avoid initiating therapy that cannot be continued, since an interrupted course may leave patients worse off [41]. Others describe dose-sparing options, though evidence for them is mostly practical advice and not trial data. Better forecasting, transparent communication from manufacturers and distribution through accredited pharmacies would reduce the worst disruptions [41]. Pharmacists in hospital and community settings are often asked to apply such rules at the counter, and clear written criteria protect both staff and patients from inconsistent decisions.

7. IMPLICATIONS FOR PRACTICE

Pharmacists can add value at several points. Before the first dose, they can screen for contraindications, review medicines that interact with delayed gastric emptying or that carry hypoglycaemia risk when combined with insulin or sulfonylureas, and explain titration [31, 32, 38]. During treatment they can monitor adherence, hydration and tolerability, reinforce dietary advice and recognise warning signs such as persistent severe abdominal pain, which may signal pancreatitis or gallbladder disease [33, 34]. After stopping, they can discuss what to expect and point patients toward continued support. Documentation is part of the service. Recording starting weight, dose steps, side effects and reasons for stopping builds a local dataset that can inform both the individual patient's care and the pharmacy's own audit,

and it supplies exactly the sort of real-world evidence that trials cannot [32, 42].

Managing expectations matters as much as managing side effects. Patients should be told that average results come from selected trial populations with lifestyle support, that some people respond poorly, and that stopping often brings weight back [7, 20, 24]. Honest conversations about duration, cost and the need for ongoing diet and activity changes lead to better decisions and fewer abandoned prescriptions. Multidisciplinary models that bring together physicians, dietitians, pharmacists and behavioural staff are consistent with guideline recommendations [4, 32]. Communication across the health team prevents duplication or conflicting advice, and it is helpful if one named clinician is responsible for the overall plan. Pharmacists can also help patients to identify credible sources of information, because misleading advertising and social media content about rapid weight loss are widespread [32, 41].

8. LIMITATIONS AND FUTURE DIRECTIONS

The evidence base has gaps that are easy to overlook given the headline numbers. Most trials ran for one to three years, enrolled mainly adults with few serious comorbidities, and used intensive lifestyle support that ordinary practice rarely matches [6, 7, 8]. People of different ethnic backgrounds, older adults, those with renal impairment and those who are pregnant or planning pregnancy are under-represented. Safety questions that need many years, including cancer, bone health and muscle function, cannot yet be answered from trials [26, 28, 35]. Quality of life, mental health and eating behaviour have received less attention than weight and metabolic markers, even though patients rank them highly. The relative weight placed on these outcomes in trial design should reflect what patients themselves value [7, 8, 32].

Further work should address long-term outcomes of continuous use, the best way to taper or maintain, and the comparative merits of the available agents in real patients, including cost per unit of benefit. Newer multi-receptor peptides and oral small

molecules are in development and may relieve some supply pressure if they prove effective [11, 15]. In the meantime, trials that include pharmacists and measure adherence, adverse events and access would answer questions that matter to daily practice [32, 41]. Economic analyses should use real-world persistence and regain data in place of trial-based assumptions, since the budget impact depends heavily on how long people actually remain on treatment [4, 24, 41]. Access research from low- and middle-income settings is almost absent from the present literature.

9. CONCLUSION

GLP-1 receptor agonists, and the dual agonist tirzepatide in particular, have delivered average weight loss that earlier drug classes could not approach, with additional cardiovascular and symptomatic benefits in selected groups [7, 8, 27]. Adverse effects are mostly gastrointestinal and manageable with slow titration, although rarer biliary, pancreatic and ocular signals need continued surveillance, and weight is regained after stopping, so treatment is probably long term [20, 24, 33, 34]. Whether those benefits persist for decades, and in people who differ from the trial populations, is not yet known.

The practical obstacles are now as important as the pharmacology. Supply shortfalls, high prices and the growth of unlicensed products affect who can be treated and how safely [4, 32, 41]. Pharmacists are well placed to support initiation, adherence and safe sourcing. Long-term outcome data, independent safety registries and fairer access models are the next things the field needs, more than another round of short efficacy trials [34, 41]. A realistic view is that these medicines are valuable but not a complete answer to obesity, which will still require prevention, food policy and long-term support.

10. ABBREVIATIONS

BMI-Body mass index, DPP-4-Dipeptidyl peptidase-4, GIP-Glucose-dependent insulinotropic polypeptide, GLP-1-Glucagon-like peptide-1, HbA1c-Glycated haemoglobin, MEN 2-Multiple endocrine neoplasia type 2, SELECT-Semaglutide effects on heart disease

and stroke in patients with overweight or obesity, MACE-Major adverse cardiovascular events, MTC-Medullary thyroid carcinoma

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12. AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

13. CONFLICT OF INTERESTS

Declared none

14. REFERENCES

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