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SEMAGLUTIDE VERSUS TIRZEPATIDE FOR WEIGHT REDUCTION: A SYSTEMATIC REVIEW AND NETWORK META-ANALYSIS

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1. INTRODUCTION

Obesity drug treatment changed character within a few years. For most of the preceding decades, pharmacotherapy delivered modest weight loss, often a few per cent of body weight, and tolerability problems or safety withdrawals were common. Liraglutide at a dose of 3.0 mg daily moved the field forward, producing a mean loss of around eight per cent over a year in the main trial [1]. Then once-weekly semaglutide at 2.4 mg raised the bar to roughly 15 per cent over 68 weeks [2], and tirzepatide, a dual receptor agonist,

Abstract

This review brings together the published evidence comparing semaglutide and tirzepatide for weight reduction, and it explains how a network meta-analysis is built and read when few direct comparisons exist. It reports no new pooled analysis or patient data. Placebo-controlled phase 3 trials show large mean weight loss with both drugs, with tirzepatide at the higher end, and a recent head-to-head trial supports that ordering. Gastrointestinal events dominate tolerability for both agents. Differences in populations, doses, durations and estimands, together with limited long-term and outcome data for tirzepatide, mean that indirect comparisons should be interpreted with caution and applied alongside individual patient factors.

reported figures near 20 per cent at the highest dose [3]. Clinicians and pharmacists are now asked, often by patients, which of the two newer drugs is better.

Answering that question is harder than it looks. For most of the period in which both drugs were studied, no trial had randomised people to one against the other for obesity. Evidence was therefore indirect: each drug had been compared with placebo in its own programme, and any statement about their relative efficacy had to bridge the two programmes through a common comparator. The statistical machinery for doing this, from the simple adjusted indirect comparison to full network meta-analysis, is well developed, but its validity depends on how similar the trials are [4, 5, 6].

A direct head-to-head trial has since reported, which sharpens the issue rather than closing it. It compared tirzepatide with semaglutide at the highest tolerated doses in adults with obesity and without diabetes, and it favoured tirzepatide for weight loss [7]. That finding sits comfortably with what earlier network estimates suggested, yet one trial cannot answer questions about older people, those with diabetes, long-term maintenance, cardiovascular outcomes or cost. This review sets out the pharmacology, the main trials, the logic and pitfalls of network synthesis, and the safety and practical points that influence choice. Key trials appear in table 1, with their grouping in fig. 1.

Table 1: Principal trials and methodological sources used to compare semaglutide and tirzepatide

Trial population	Reported finding	Ref.
STEP 1 obesity, no diabetes	Semaglutide 2.4 mg gave about 15 per cent loss at 68 weeks versus about 2 per cent on placebo.	[2]
STEP 2 obesity with diabetes	Weight loss was smaller than without diabetes but exceeded placebo.	[8]
STEP 4 maintenance	Continuing semaglutide gave further loss; switching to placebo led to regain.	[9]
STEP 8 versus liraglutide	Weekly semaglutide produced greater loss than daily liraglutide 3.0 mg.	[10]
SURMOUNT-1 obesity, no diabetes	Tirzepatide 5, 10 and 15 mg gave dose-related loss, up to about 21 per cent at 72 weeks.	[3]

Trial population	Reported finding	Ref.
SURMOUNT-2 obesity with diabetes	Substantial loss exceeding placebo, though less than in people without diabetes.	[11]
SURMOUNT-4 maintenance	Continued tirzepatide gave further loss; placebo substitution led to marked regain.	[12]
SURPASS-2 diabetes	Tirzepatide beat semaglutide 1 mg for glycated haemoglobin and weight.	[13]
SURMOUNT-5 obesity, no diabetes	Tirzepatide produced about 20 per cent loss versus about 14 per cent with semaglutide.	[7]
Adjusted indirect comparison	Differences estimated through a common comparator rely on transitivity.	[4, 6]
Ranking and heterogeneity	SUCRA and I ² need intervals and clinical context to interpret.	[5, 14]

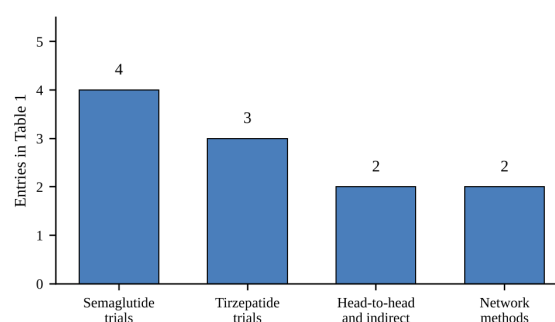


Fig. 1: Number of entries in table 1 by type of evidence

Because the title refers to a systematic review and network meta-analysis, a clarification is needed at the outset. No new literature search with counts, no new data extraction and no new pooled model are reported here. The text synthesises published trials, previously published meta-analyses and methodological papers, and quotes numbers as the original authors reported them. Its purpose is to show what the evidence can and cannot support, and to help readers appraise any network analysis that compares these two drugs. Where the evidence is thin or comes mainly from one trial, that is stated plainly rather than smoothed over, since the audience includes pharmacists who must explain the uncertainty to patients and prescribers.

It helps to remember how recent this comparison is. Semaglutide was first developed for type 2 diabetes at lower doses

and later studied at 2.4 mg for weight management, while tirzepatide was developed for diabetes and then obesity within a few years. The two obesity programmes therefore ran in overlapping periods, with different sponsors, different design choices and different ways of defining the primary analysis. Those choices matter later when trials are lined up side by side in a network, because the apparent differences between drugs can partly reflect differences between programmes [8, 11, 15].

2. PHARMACOLOGY OF THE TWO AGENTS

Semaglutide is a long-acting analogue of glucagon-like peptide-1. Amino acid substitutions protect it from degradation by dipeptidyl peptidase-4, and a fatty diacid side chain promotes albumin binding, which extends the half-life to roughly a week and allows weekly injection [16]. GLP-1 receptor activation reduces appetite and food intake through hypothalamic and brainstem pathways, slows gastric emptying and enhances glucose-dependent insulin secretion [17]. In obesity the central effects are thought to account for most of the weight loss, with patients describing earlier satiety, fewer cravings and smaller portions rather than any dramatic change in metabolic rate.

Tirzepatide is a single peptide that activates both the glucose-dependent insulinotropic polypeptide (GIP) receptor and the GLP-1 receptor. It was engineered from the GIP sequence, with a fatty acid chain for albumin binding and, in cell assays, greater potency at the GIP receptor than at the GLP-1 receptor [18]. How GIP signalling adds to weight loss is still debated. Proposed contributions include central effects on appetite, improved tolerability through reduced nausea and effects on adipose tissue handling of lipids, but human evidence for each is incomplete [19, 20]. The dual mechanism is the usual explanation for the larger average effect seen in trials.

Clinical pharmacology studies provide a bridge between mechanism and trial outcomes. In adults with type 2 diabetes, tirzepatide improved markers of pancreatic islet function and insulin sensitivity more

than placebo and, in some measures, more than semaglutide at the doses studied [21]. These were short mechanistic trials, so they cannot predict long-term weight outcomes. Still, they hint that the two drugs do not act identically even though both engage the GLP-1 receptor. For prescribers, the practical points are weekly subcutaneous dosing for both, stepwise dose escalation over months, and similar handling and counselling needs.

Dose structure complicates comparisons. Semaglutide for weight management is escalated to 2.4 mg weekly, whereas tirzepatide is escalated in steps to 5, 10 or 15 mg, and the main trial allowed participants to remain at a lower dose if the higher one was not tolerated [2, 3]. A comparison of drug against drug therefore needs to specify which tirzepatide dose is meant. Network meta-analyses often present each dose as a separate node, or sometimes lump doses together, and the choice can materially alter the estimated difference to semaglutide, which is one reason published estimates are not interchangeable [5, 15].

Peptide drugs share some practical features worth knowing before first prescription. They are given by injection, usually with a prefilled pen, and storage conditions matter before first use. Missed doses are generally managed by a window rule rather than by doubling. Absorption is not meaningfully altered by injection site, and renal or hepatic impairment has limited effect on exposure. Patients who stop treatment lose the pharmacological effect within weeks, and this has important consequences for weight regain, which is discussed later in the context of maintenance and withdrawal [12, 22].

3. EVIDENCE FROM RANDOMISED TRIALS

The semaglutide programme for weight management is known as STEP. In the first trial, adults with overweight or obesity and without diabetes lost on average about 15 per cent of body weight over 68 weeks on semaglutide 2.4 mg, against about 2 per cent on placebo, with both groups receiving lifestyle advice [2]. In people with type 2 diabetes the effect was smaller, near ten per cent against three per cent [8]. Adding

intensive behavioural therapy produced a larger loss still [23], and a two-year trial showed that weight loss was sustained rather than regained during continued treatment [24]. The overall pattern was consistent across the programme [15].

The tirzepatide programme, called SURMOUNT, followed a similar structure. In the first trial, adults with obesity or overweight without diabetes lost around 15, 19 and 21 per cent of body weight at 72 weeks on 5, 10 and 15 mg respectively, against about 3 per cent on placebo [3]. In adults with obesity and type 2 diabetes, weight loss was smaller but still substantial and clearly exceeded placebo [11]. A trial that started tirzepatide after intensive lifestyle intervention showed a further large reduction [25]. Across the programme the dose-response relationship was visible, and tolerability was acceptable to most participants.

Maintenance and withdrawal designs are informative. In STEP 4, participants who reached a stable dose and were then randomised to continue semaglutide lost more weight, while those switched to placebo regained a large part of what they had lost [9]. SURMOUNT-4 showed the same asymmetry with tirzepatide, with continued treatment giving further loss and placebo substitution giving substantial regain [12]. A follow-up of STEP 1 reported that, after withdrawal, participants regained about two-thirds of their prior weight loss within a year, along with a return of cardiometabolic risk factors toward baseline [22]. Both drugs therefore behave like chronic therapies.

Head-to-head evidence comes from two sources. The first is the SURPASS-2 trial in adults with type 2 diabetes, which compared tirzepatide with semaglutide 1 mg and found that all tirzepatide doses produced greater reductions in glycated haemoglobin (HbA1c) and body weight, although the semaglutide dose was lower than that used for obesity [13]. The second is SURMOUNT-5, in adults with obesity without diabetes, in which tirzepatide produced a mean weight loss of about 20 per cent against about 14 per cent with semaglutide at 72 weeks [7]. Both found a consistent direction of effect in favour of

tirzepatide.

Other comparators help to place the two drugs. Weekly semaglutide 2.4 mg was compared directly with daily liraglutide 3.0 mg in the STEP 8 trial and gave substantially greater weight loss [10]. Earlier liraglutide trials against placebo provide the link between old and new generations of agents, which is exactly how indirect comparison via a shared comparator works [1, 6]. The response is not uniform. In every programme, a minority of participants lost little weight, and a minority lost far more than the mean, which is why average figures should not be quoted to patients as promises [2, 3, 15].

Cardiometabolic outcomes extend the picture beyond the scale. Semaglutide has trial data on cardiovascular events: a diabetes outcome trial found fewer major adverse cardiovascular events (MACE) than placebo [26], and the SELECT trial extended this to adults with established cardiovascular disease and obesity without diabetes [27]. Meta-analysis of GLP-1 receptor agonist outcome trials supports a class effect on cardiovascular and kidney outcomes in diabetes [28]. For tirzepatide, outcome evidence was less mature at the time of the main weight trials, so claims of superior cardiovascular protection cannot be drawn from weight loss figures alone [13, 29].

The time course of weight loss is worth understanding because trial endpoints capture only one point on it. With semaglutide 2.4 mg, mean weight fell steeply in the first months and then flattened, so that the curve was close to a plateau by the second year, as the two-year STEP 5 results confirmed [2, 24]. With tirzepatide, loss continued over a similar period before levelling off at its higher plateau [3]. Because the endpoints were taken at different times, 68 weeks for one programme and 72 for the other, a naive subtraction of headline figures slightly favours the drug with the longer trial. Time-matched or model-based estimates are more reliable.

Categorical responses add detail that mean values hide. Trials reported the proportion of participants achieving at least 5, 10, 15 or 20 per cent weight loss. At the lower thresholds the large majority of people on either drug

met the target, whereas at 20 per cent or more the difference between the drugs became pronounced, with tirzepatide reaching it in a far larger share of participants [2, 3, 7]. Secondary outcomes such as waist circumference, blood pressure, lipids and glycaemia improved with both drugs and tracked the degree of weight loss [11, 15]. Responder analyses are therefore helpful in conversations about what a given patient might expect.

4. NETWORK META-ANALYSIS: METHODS AND CAUTIONS

A network meta-analysis (NMA) combines direct and indirect evidence within a single model, so that treatments never compared head to head can still be ranked. The basic building block is the adjusted indirect comparison, in which the difference between A and B is estimated from the difference between A and a common comparator C and between B and C [6]. Mixed treatment models generalise this to many treatments at once and are usually fitted in a Bayesian or frequentist framework [4]. Good-practice guidance covers how such analyses should be conducted and interpreted [30], and a dedicated extension of the PRISMA reporting statement exists for them [31].

The key assumption is transitivity: that the trials are similar enough in everything that modifies the treatment effect for indirect inference to be valid. For obesity drugs, effect modifiers include baseline body mass index (BMI), diabetes status, sex, trial duration, dose, background lifestyle intervention and the way analyses handle people who stop treatment. When STEP and SURMOUNT trials are lined up, these factors differ somewhat, which is why a purely indirect estimate of the gap between the drugs is uncertain. Statistical tests for inconsistency compare direct and indirect estimates where both exist, but they have low power in sparse networks [6, 32].

Heterogeneity is another recurring issue. The I^2 statistic describes the proportion of variation across studies beyond chance, and values should be read together with their confidence interval and with the clinical diversity of the trials [14]. Random-effects

models, long used in meta-analysis, allow effects to vary between studies but give less weight to large trials than fixed-effect models [33]. With only a few trials per drug, estimates of between-study variance are imprecise, so the choice of model and prior can move the result. Sensitivity analyses that exclude particular trials or doses are a sensible part of any report.

Risk of bias assessment is the third pillar. The Cochrane risk-of-bias approach, set out in the handbook, judges randomisation, deviations from intended interventions, missing outcome data, outcome measurement and selective reporting [34], and earlier meta-epidemiological work showed why: inadequate allocation concealment and blinding were associated with exaggerated treatment effects [35]. The large industry-sponsored phase 3 trials of both drugs are generally well conducted, but missing data are an important area, because dropout was higher in placebo groups and was handled with specific statistical approaches. Reporting of both treatment-policy and trial-product estimands differs between trials, and mixing the two in one network would bias comparisons toward the drug whose trials used the more favourable estimand [2, 3].

Ranking metrics need care. The surface under the cumulative ranking curve, or SUCRA, converts rank probabilities into a single number per treatment and is widely used to present results [5]. It is easy to over-read. A treatment can have a high SUCRA value because it is probably slightly better than its neighbours, even when the actual difference is small and the intervals overlap. Readers should look at the estimated mean differences and their intervals, together with the certainty of evidence, rather than at rankings alone. In a network with two high-performing drugs and one placebo, rank probabilities simply restate the point estimates.

The choice of outcome and effect measure influences how comparable trials appear. Most reports use the percentage change in body weight from baseline, whereas others express results as the difference in kilograms between active and placebo arms. These are not interchangeable because baseline weights

differ between populations, and a given percentage translates into more kilograms in a heavier cohort. Networks usually pool mean differences on one scale, and the choice of scale can change which comparisons look consistent [4, 5, 14]. Handling of missing data, notably multiple imputation versus last observation carried forward, adds yet another source of divergence between trial reports.

Consistency between direct and indirect evidence can now be examined empirically. When the head-to-head diabetes trial and the head-to-head obesity trial are added to a network, analysts can compare their results with what the indirect route predicted and test for disagreement using node-splitting or design-by-treatment approaches [6, 32]. Agreement in direction, as seen here, strengthens confidence in the indirect estimates, but it does not prove transitivity for other populations or outcomes. Network analysts are advised to report the extent of inconsistency, to investigate its sources and to avoid presenting a pooled estimate when disagreement is large [7, 13, 32].

A final methodological caution concerns the evolution of a network over time. When a direct trial appears, the network changes: previously indirect evidence is now supplemented by randomised comparison, and the combined estimate generally shifts toward the direct result. Reviews published before the direct trial should therefore be read as interim estimates. Living network meta-analysis is one proposed answer, but it requires disciplined updating and transparent change logs. For readers, the practical lesson is to check the date of the last search and whether the newest direct evidence is included before relying on a published ranking [7, 31, 32].

5. SAFETY AND TOLERABILITY

Gastrointestinal symptoms are the dominant adverse effects of both drugs. Nausea, vomiting, diarrhoea and constipation are common during dose escalation and usually mild to moderate, with a minority of patients stopping treatment because of them. A systematic analysis of GLP-1 receptor agonist trials showed that these symptoms are frequent across the class and depend on dose

and escalation pace [36]. The semaglutide and tirzepatide trials reported broadly similar patterns, with symptoms concentrated in the escalation phase and tending to diminish thereafter [2, 3]. Slow titration, small meals and avoiding fatty food are the usual practical advice.

Rarer events attract more attention than their frequency deserves, yet they should not be ignored. A meta-analysis of randomised trials linked GLP-1 receptor agonists to a higher risk of gallbladder and biliary disease, with the risk higher at higher doses, longer treatment and in trials aimed at weight loss [37]. Observational data suggested increased risk of pancreatitis, gastroparesis and bowel obstruction in people using GLP-1 receptor agonists for weight loss compared with another weight drug [38]. Such analyses cannot prove causation, and absolute risks are small, but they support counselling patients about persistent severe abdominal pain.

Several aspects of safety relate to the rate and composition of weight loss. Rapid loss increases gallstone formation, and some of the weight lost is lean mass rather than fat, a feature of caloric restriction in general. Adequate protein intake and resistance exercise are commonly recommended, though trial evidence on mitigation is limited. Exercise alone or combined with liraglutide improved maintenance of weight loss and fitness in one randomised trial, which suggests lifestyle components retain value when drug treatment is used [39]. Comparable trials combining exercise with tirzepatide or semaglutide are needed.

Tolerability comparisons between the two drugs are less certain than efficacy comparisons. Event rates depend on definitions, on titration schedules and on whether discontinuation was counted for any reason or for adverse events specifically. The head-to-head trial reported similar patterns of gastrointestinal events in the two arms, though the study was designed for weight rather than for rare safety outcomes [7]. Longer follow-up and surveillance data are required, particularly for tirzepatide, whose outcome trials were still maturing when most weight data were published [13, 29]. A claim of superior tolerability for either drug is not

currently justified, and the wording of any patient information should reflect that uncertainty.

Discontinuation and adherence data link safety to effectiveness. In the main trials most participants completed treatment, and the proportion stopping because of adverse events was higher than with placebo but still a minority [2, 3]. In routine practice the situation is less favourable, because people face costs, supply gaps and fewer clinic contacts. Dose reduction, slower titration or a temporary pause are often more helpful than stopping altogether, yet they are rarely evaluated in trials. How these pragmatic adjustments affect eventual weight loss is unknown, which makes it hard to give precise advice when a patient cannot tolerate the labelled maintenance dose [2, 7].

6. PRACTICAL IMPLICATIONS

The practical reading of the evidence is that both drugs are effective, tirzepatide probably more so on average, and that the size of the difference is moderate relative to the size of each drug's effect against placebo. For an individual, however, other factors may count for more than a few percentage points of average weight loss. These include tolerability during escalation, injection burden, supply and cost, comorbidities such as diabetes or established cardiovascular disease, and patient preference. Where cardiovascular outcome data exist for one agent in a defined population, that can reasonably tip a decision [7, 27, 40].

Pharmacists have several roles in this area. They can explain escalation schedules and what to do after missed doses, counsel on expected side effects and when to seek help, check interacting medicines, and reinforce the lifestyle component that all trials included. They also have a part in discussing duration, because the withdrawal data indicate that stopping treatment typically leads to substantial regain [9, 12, 22]. Clinical guidelines for obesity management place pharmacotherapy as an adjunct to nutrition, activity and behavioural support rather than as a substitute for it [15, 40].

Access is a practical limitation that sits outside the trial results. Both drugs are

expensive, supply constraints have affected availability in several countries, and reimbursement varies with indication. Compounded or unlicensed products have appeared where supply is short, raising quality and dosing concerns. Cost-effectiveness depends on how long treatment continues, on the avoided complications and on price, none of which can be inferred from trial weight loss. Health systems therefore need to prioritise patients with the greatest expected benefit, such as those with serious obesity-related complications, and to plan follow-up so that effects are sustained [12, 40]. Without such planning, the gap between what trials show and what routine care achieves is likely to widen.

Adults with type 2 diabetes need a separate thought. In that group the weight loss achieved is smaller, but the glycaemic effect is a main treatment goal, and both drugs lower HbA1c substantially [8, 11, 13]. The head-to-head diabetes trial favoured tirzepatide for both outcomes at the doses tested [13], yet semaglutide has the longer record of cardiovascular outcome benefit in people with diabetes [26, 28]. Prescribers may reasonably prefer one drug for its cardiovascular evidence and the other for its larger effect on weight, and the decision turns on which outcome matters most to the patient.

Review and stopping rules are also practical matters. Obesity management guidance recommends setting a response target, assessing progress after an adequate period at the maintenance dose, and reconsidering treatment if weight loss is minimal [15, 40]. With drugs that need months of escalation, the assessment point should be based on time at the target dose, not on the start date. If the drug is stopped for any reason, patients need a plan for diet, activity and monitoring, because the withdrawal data show that weight and cardiometabolic risk factors tend to drift back toward baseline [9, 12, 22].

7. LIMITATIONS AND FUTURE DIRECTIONS

The evidence summarised here has clear limits. Most data come from large industry-sponsored phase 3 trials with

carefully selected participants, who differ from real-world populations in age, comorbidity and adherence. Follow-up was one to two years, whereas obesity treatment is probably lifelong. Only one head-to-head trial in people without diabetes has been reported, and findings on older adults, adolescents and people with severe renal impairment are limited. The estimates quoted should be read as averages within trial conditions, and published network analyses inherit all these weaknesses and add the uncertainty of indirectness [5, 6, 7].

Future work should concentrate on a few questions. Longer comparative trials, including cardiovascular, renal and mortality outcomes for tirzepatide, are needed before outcome claims can be matched with those for semaglutide. Studies of how best to maintain weight loss, whether through lower maintenance doses, intermittent treatment or combination with exercise, would address the regain problem [12, 22, 39]. Pragmatic head-to-head trials and real-world registries could show whether trial differences survive routine care. Methodologically, network analyses should state their estimands, handle dose explicitly and update as direct evidence accumulates [31, 32].

8. CONCLUSION

The best available evidence places tirzepatide ahead of semaglutide for average weight reduction in adults with obesity, and both agents are well ahead of earlier drugs and of placebo [1, 2, 3, 7, 10]. The advantage appears in a direct trial and in the indirect network estimates that preceded it, and it is consistent with the dual-receptor pharmacology [7, 18, 21]. Even so, the gap is smaller than the distance between either drug and placebo, and it applies to averages rather than individuals [5, 6, 15].

Beyond efficacy, the choice rests on matters that network analyses address poorly: tolerability during escalation, cardiovascular outcome evidence, cost, access and the person's own priorities, and these are the matters on which a pharmacist's judgement is most useful [27, 36, 38, 40]. Both drugs behave as long-term treatments, since stopping leads to substantial regain [12, 22].

Readers of any network meta-analysis in this field should check transitivity, dose handling, estimands and the date of the last search before accepting a ranking. Where randomised controlled trials (RCTs) with direct comparison become available, they should take precedence over modelled estimates [7, 31, 32].

9. ABBREVIATIONS

BMI-Body mass index, GIP-Glucose-dependent insulinotropic polypeptide, GLP-1-Glucagon-like peptide-1, HbA1c-Glycated haemoglobin, MACE-Major adverse cardiovascular events, PRISMA-Preferred Reporting Items for Systematic Reviews and Meta-Analyses, RCT-Randomised controlled trial, SUCRA-Surface under the cumulative ranking curve, STEP-Semaglutide Treatment Effect in People with obesity, SURMOUNT-Tirzepatide obesity trial programme, NMA-Network meta-analysis

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All the authors have contributed equally.

12. CONFLICT OF INTERESTS

Declared none

13. REFERENCES

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