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BRIEFING PAPER

Isca Evidence, University of Exeter: August 2025

GLP-1 RAs for weight loss: the quantity, quality and findings of network meta-analyses evaluating their effectiveness.

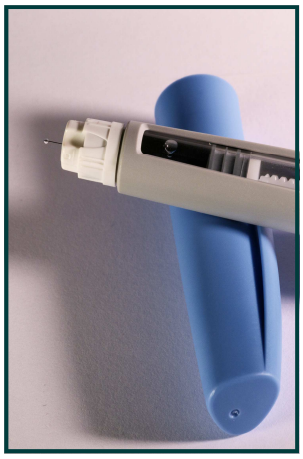
Obesity is a widespread chronic disease that is associated with increased risks of serious conditions, such as cardiovascular disease and stroke[1]. It is therefore unsurprising that the latest generation of anti-obesity drugs have garnered lots of attention. These **Glucagon-like peptide-1 receptor agonists (GLP-1 RAs)** work against obesity by increasing insulin secretion, slowing gastric emptying and reducing appetite[2]. There is an abundance of evidence that discusses the effectiveness and safety of these drugs, including numerous network meta-analyses comparing different GLP-1 RAs.

We therefore undertook a scoping review to summarise the findings, and critically appraise the quality, of network meta-analyses. We were also interested in the safety and effectiveness of GLP-1 RAs, and wanted to identify evidence gaps.

A network meta-analysis (NMA) is a method that compares several treatments at once, even if some haven't been directly compared in studies. It uses a network of interventions to connect the results and figure out which work best overall.

Key Findings

- Of **22 included NMAs**, **eight** were **low or critically low quality** and were excluded from further analysis. The **remaining 14** were of **moderate quality**, demonstrating a lack of rigorous methodology.
- The **most effective drugs at six months** were **semaglutide** (0.5mg and 1.0mg) and **tirzepatide** (10mg and 15mg), which were associated with 5.5kg to 8kg and 9kg to 12kg of weight loss over placebo respectively.
- **Semaglutide (2.4mg) was also effective** when looking at combined time points (associated weight loss over placebo of 11.5kg to 12.5kg).
- All drugs had side effects (commonly nausea and upset stomach). Some more serious effects caused people to stop treatment, though no one drug stood out as worse than others. There was a **lack of information** about **long-term effectiveness** and **safety.**



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This is a high-level overview of our research to inform decision-making. Further outputs including plain language summaries and academic papers are available:

https://doi.org/10.3310/SKHT8119

In the UK, 26% of men and 29% of women are classified as obese[3].

The economic cost to the UK National Health Service by obesity and related illnesses is estimated at £6.1 billion a year[4].

We found that the size of the network meta-analyses literature featuring GLP-1 RAs and weight loss outcomes has almost doubled in the last year.

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Why did we do this review?

Review rationale—the 'why'

1. There is abundant evidence about the effectiveness and safety of GLP-1 RAs for obesity, including publication of numerous NMAs in recent years.

2. The quality and scope of these recently published NMAs is variable.

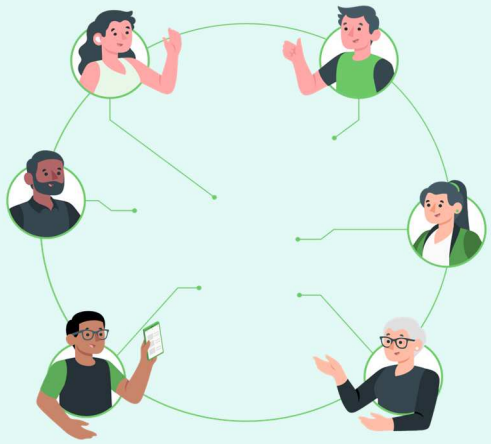
3. **Therefore,** this study aims to critically overview the findings of recent NMAs analysing weight loss outcomes, with a focus on evaluating the evidence for effectiveness and safety of GLP-1 RAs authorised in the UK (such as semaglutide or liraglutide).

Patient and Public Involvement/Engagement

This review was strengthened by the involvement of a group of around 15 public collaborators, called PERSPEX. This culturally, geographically and demographically diverse group meet monthly, and brought carer, patient, or public perspectives to Isca Evidence work (https://www.exeter.ac.uk/research/groups/medicine/esmi/workstreams/perspex/).

The group were involved at multiple stages, including contributing to the protocol by reviewing a plain English version. The review was discussed at two of the regular monthly meetings, and brought up questions and concerns about potential harms and side effects of the drugs. Safety and maintenance of weight loss, and industry sponsorships were also mentioned.

This provided context of patient and carer concerns for the review team, and promoted discussions about incorporating harms and side effects.



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Overview of the evidence

- 22 systematic reviews with network meta-analyses met our inclusion criteria.

- **14 studies** were rated of **moderate quality** and were prioritized for synthesis. **six reviews** were assessed as **low quality** and **two** of critically **low quality**. **No included reviews** were assessed as **high quality.**

- PROGRESS-Plus criteria for further analyses were used in eight papers, but only one study analysed results based on race/ethnicity.

GLP-1 RA studied	Number of reviews
Semaglutide	9
Liraglutide	11
Tirzepatide	2
Exenatide	8
Dulaglutide	2
Lixisenatide	2
GLP-1 RAs (as a single intervention)	3

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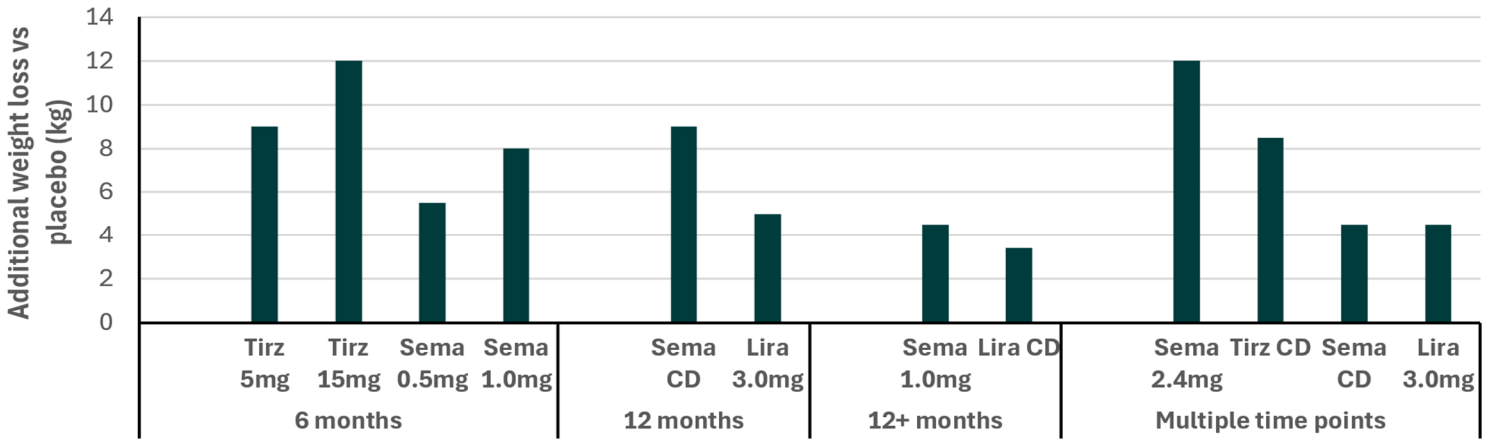
What did we find?

Effectiveness of semaglutide, liraglutide and tirzepatide vs placebo

Three GLP 1 RAs are currently licensed for use in the UK for weight loss —semaglutide, liraglutide and tirzepatide— and therefore these will be prioritised in the reporting of our findings. Firstly, we compared the drugs versus placebo:



Sema = semaglutide / Lira = liraglutide / Tirz = Tirzepatide / CD = combined dose (where a variety of doses were combined to one variable)

Comparative effectiveness of semaglutide, liraglutide and tirzepatide

- **6 months:** **Tirzepatide** outperformed semaglutide, with the largest difference being 5.6kg between Tirzepatide 15mg and Semaglutide 0.5mg
- **12 months:** **Semaglutide CD** was associated with 4kg greater weight loss than Liraglutide 3.0mg
- **12+ months:** **Semaglutide 1mg** outperformed Liraglutide 0.6mg by 3.0kg
- **Multiple time points:** **Tirzepatide CD, Semaglutide 2.4mg and Semaglutide CD** outperformed comparators

Safety of GLP-1 RAs

- Serious adverse events (SAEs) were more common with subcutaneous semaglutide 2.4mg than alternatives in one review
- Total adverse events (AEs) were more common with semaglutide 1.0mg and 2.4mg versus placebo.
- SAEs and AEs were more common taking tirzepatide 15mg than placebo, whilst tirzepatide 5mg had a higher risk of specifially SAEs and tirzepatide 10mg specifically AEs.
- SAEs or AEs were no more common for all doses of liraglutide versus placebo, apart from liraglutide 3.0mg.

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What are the implications of this review?

This scoping review provides the first overview of either effectiveness or safety network meta-analyses for GLP-1 RAs that have been approved for use in the UK. We focused on the effectiveness of these drugs for weight loss and safety outcomes, particularly the three drugs currently approved for weight loss in the UK (semaglutide and liraglutide, and tirzepatide).

An update search was carried out on the 26th September 2024, and 14 new NMAs were identified, demonstrating how fast this field is evolving. There were multiple novel comparisons, notably tirzepatide and semaglutide 2.4mg, however due to the volume of new evidence discovered during the project only a brief review was possible.

Semaglutide, liraglutide and tirzepatide appear to be effective drugs for weight loss. Tirzepatide 10 mg and 15 mg, and semaglutide 2.4 mg are associated with the greatest effects and have similar safety profiles. Despite a large volume of recent network meta-analyses evidence, findings are inconsistent, especially for safety outcomes, and the methodological rigour could be improved.

Future research

- Whilst network meta-analyses give a good indication of how the GLP-1 RAs compare, head to head trials of the two most promising options (tirzepatide vs semaglutide 2.4 mg) should be carried out to determine relative effectiveness and safety.
- Long-term effectiveness and safety must also be prioritised as there is little data post 72 weeks.
- A living network meta-analysis may be an appropriate next step, with the publication rate of de novo network meta-analyses exceeding availability of new trial data.

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Isca Evidence

We are one of 13 research groups in the UK commissioned by the National Institute for Health and Care Research Evidence Synthesis Programme to address knowledge gaps or to answer a specific need for health, public health and social care audiences.

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