What is the quantity, quality and scope of recent network meta-analyses evaluating the effectiveness of Glucagon-like peptide-1 receptor agonists for weight loss in obese adults? Protocol for a scoping review of network meta-analyses

Authors: Nunns M, Febrey S, Buckland J, Abbott R, Whear R, Bethel A, Shaw E, Boddy K, Thompson Coon J, Melendez-Torres GJ

Address: Exeter Evidence Synthesis Centre, University of Exeter Medical School, University of Exeter, St Lukes Campus, Exeter, Devon, EX1 2LU

1. Background

Obesity is a chronic disease associated with increased risks of developing several serious and potentially life-threatening conditions including cardiovascular disease, stroke, and type 2 diabetes.[1] The prevalence of obesity in the UK is rising, with 27% of adults in England considered obese in 2017 [2]: this figure expected to rise to 35% 2030.[3]

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) are drugs used in the management of obesity and type 2 diabetes mellitus (T2DM), authorised by NICE for use in the UK. There is an abundance of evidence about the effectiveness of GLP-1 RAs for the management of both T2DM and obesity, including several network meta-analyses (NMAs). The purpose of this review is to summarise, critically evaluate and update (where possible and useful) NMAs which evaluate the effectiveness of GLP-1 RAs for weight loss in obese patients.

1.2 Overall aims and objectives

- To identify and collate the most recent (published since 2020) NMAs which evaluate the effectiveness of GLP-1 RAs for weight loss.
- To critically appraise the included NMAs.
- To provide an overview of the quality and findings of existing NMAs, and to identify any pertinent gaps in the evidence.
- To consider the value of updating the most recent, comprehensive and high-quality NMA(s) with trials published since the search date(s) in those NMA(s). If this is of value, a new protocol will be registered with respect to that project.

1.3 Research questions

1) What is the quantity, quality and scope of recent network meta-analyses evaluating the effectiveness of Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) for weight loss in obese adults?

2) What is the effectiveness of GLP-1 RAs for weight loss in obese patients, according to recent, high quality network meta-analyses?

3) What adverse events are associated with GLP-1 Ras in obese patients, according to recent, high quality network meta-analyses?

2. Methods

2.1 Identification of studies

Search strategy

The search will include both free text and controlled vocabulary searching, when available and relevant. We will search for both drug classes and individual drugs which will be based on products licenced in the UK as of May 2023, for any indication.

Draft Medline search strategy

1 network meta-analysis.mp. or exp Network Meta-Analysis/

2 (Semaglutide or Liraglutide or Tirzepatide or Lixisenatide or Exenatide or Dulaglutide).tw. OR exp Glucagon-Like Peptide-1 Receptor/ag [Agonists] OR (GLP-1 and (agonist or analogue)).mp.

3 1 and 2

Information sources

The following databases will be searched from inception to present:

- MEDLINE (Ovid)
- EMBASE (Ovid)
- Cochrane Database of Systematic Reviews (Wiley)
- Epistemonikos

Supplementary methods

We will seek additional relevant records by carrying out citation searching (forward and backwards) of the included NMAs in Web of Science and Scopus. The results of the citation searching will be downloaded into Endnote, de-duplicated against the database searches then a simple search will be carried out with the term 'network'.

2.1.1 Inclusion and exclusion criteria

The inclusion and exclusion criteria (according to PICO framework) to be applied to the studies identified through the search strategy are detailed below:

Participants/population:

Adults (18 or above) with BMI >25

Intervention:

NMAs which include trials of the following GLP-1 RAs (authorised by NICE for use in the UK):

- Semaglutide (also known as Ozempic, Rybelsus, Wegovy)
- Liraglutide (also known as Victoza, Saxenda)
- Tirzepatide (also known as Mounjaro)
- Exenatide (also known as Byetta)
- Dulaglutide (also known as Trulicity)
- Lixisenatide (also known as Lyxumia)

Any dosage or mode of delivery (e.g. oral or subcutaneous) is of interest. Interventions may be drug-only or as part of multimodal interventions, for example GLP-1 RA with dietary modifications.

Comparator(s)/control

Another GLP-1 RA or placebo

Outcomes

A measure of weight loss such as change in mass or BMI from baseline is required for inclusion.

Other relevant outcome measures related to weight loss, such as body composition, will be extracted but are not necessary for inclusion.

Where NMAs report trial results relating to safety (for example adverse events, deaths, discontinuation or withdrawal on safety grounds etc.) these will be extracted, but are not necessary for inclusion.

Study design

Systematic reviews with network meta-analyses.

Date limit

Articles published in 2020 or later.

Geographical Context

Trials must be conducted in a context relevant to the UK. This will be assessed on a case-by-case basis, in discussion with key stakeholders.

2.1.2 Process for applying inclusion criteria.

The title and abstract of each record retrieved by the search will be screened by two independent reviewers to identify records that are clearly irrelevant. Disagreements will be resolved by discussion. After this stage, the full text of each remaining record will be screened by two independent reviewers to determine inclusion. Disagreements will be resolved through discussion, with a third reviewer acting as arbiter if necessary. Articles excluded at the full text screening stage will be coded to indicate the first reason for exclusion.

2.2 Critical appraisal

Each included review will be critically appraised using a modified version of AMSTAR-2. This version will include items 1-10, 13, 14, and 16, thus omitting questions related to synthesis and focusing on methodological rigour when conducting the systematic review element. Reviews that contain no fatal flaws (critical items: 2 (protocol), 4 (search), 9 (risk of bias assessment)) will be subjected to full data extraction and further appraisal using the International Society of Pharmacoeconomics and Outcomes Research (ISPOR) checklist for assessing the reliability of NMAs.

The findings of assessment with the ISPOR checklist will be used to inform the discussion of findings.

2.3 Data Extraction

Data extraction of key information will be performed on studies included in the review. For each included record, one reviewer will complete data extraction, and a second reviewer will check the extracted data for accuracy.

Data will be extracted in relation to the following:

- Author details (author names, title, date of publication, doi etc)
- Funding and conflict of interest information (funder of NMA, whether funding was evaluated within primary studies, whether conflicts of interest were declared)
- Review inclusion criteria relating to population (e.g. BMI, gender, age, comorbidities)
- Observed sample characteristics (trial locations (country), number of trials included, mean/SD/range age of sample, gender, sample size, mean/SD/range BMI, relevant comorbidities etc)
- NMA Intervention details (GLP-1 RAs included, dose/regime, mode of administration, duration of intervention, other intervention components etc)
- NMA Comparator details (name/type of comparator, duration, key components etc)
- Outcomes (all included outcomes)
- Details of weight loss outcome (how evaluated/calculated, time points etc)
- Relevant inequalities (any PROGRESS Plus criteria relevant to the NMA)
- Findings. For studies not prioritised for ISPOR evaluation, a text summary of findings relating to weight loss will be provided. For prioritised NMAs, we will extract effect sizes for change in weight loss outcomes for each comparison of a GLP-1 RA vs comparator of interest.
- NMA characteristics. For NMAs not prioritised for evaluation with ISPOR, the framework (e.g. Bayesian, frequentist), model (e.g. fixed or random effects) and effect measure type (e.g. mean difference, odds ratio etc) will be reported. Prioritised NMAs will be subject to detailed methodological evaluation with ISPOR in addition to these items being captured.

2.4 Synthesis

Extracted data will be tabulated and summarised with accompanying text. The synthesis will describe key characteristics of included reviews and NMAs, any areas of overlap or gaps in the evidence, the quality of evidence, and the findings of NMAs in terms of the effectiveness of GLP-1 RAs on weight loss. Forest plots will be used to summarise comparisons explored by multiple NMAs. Findings relating to safety will be grouped by type of outcome and described using narrative synthesis.

3. PPIE

The project will be discussed with members of the PERSPEX engagement group at intervals throughout. The review team will ask for feedback on the proposal, progress and findings.

4. Dissemination and timeline

A report will be produced and publication as a journal article will be considered. We anticipate the review will take 3 months to complete, from the point the protocol is approved. In the event that it is feasible and beneficial to produce an updated NMA, a new protocol with expected timeline will be produced.

5. Funding

This review is funded by the NIHR Evidence Synthesis Programme.

6. References

1. Research NIfHaC. *Managing obesity in men*. 2016. URL: https://evidence.nihr.ac.uk/collection/managing-obesity-in-men/ (accessed 01.06.2023).
2. NHS Digital. *Statistics on obesity, physical activity and diet - England*. 2017. URL: https://digital.nhs.uk/data-and-information/publications/statistical/statistics-on-obesity-physical-activity-and-diet/statistics-on-obesity-physical-activity-and-diet-england-2017 (accessed 01.06.2023).
3. The Organisation for Economic Co-operation and Development (OECD). *Obesity Update*. 2017. URL: https://www.oecd.org/els/health-systems/Obesity-Update-2017.pdf (accessed 01.06.2023).