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

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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. National Institute for Health and Care Research (NIHR). *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).

Which aspects of digital interventions to support weight loss programmes are associated with success? Protocol for a systematic review with component network-meta-analysis.

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Background

Obesity is a complex chronic disease associated with increased risks of developing several serious and potentially life-threatening conditions including cardiovascular disease, stroke, and type 2 diabetes[4]. It is a growing global health problem. The prevalence of obesity in the UK is rising, with 27% of adults in England considered obese in 2017 [5]; this figure expected to rise to 35% by 2030[6].

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs), such as semaglutide and liraglutide, are drugs authorised in the UK by NICE for the management of obesity. These are recommended for some adults with obesity, as a treatment option alongside a reduced-calorie diet and increased physical activity. Access to these drugs is within specialist weight management services only.

Not everyone who is eligible for these drugs may be able to access these weight management services within secondary care and there are national variations with how these services are delivered[7]. Mobile/digital technologies may be useful platforms to assist with weight management. Digital interventions may offer more flexibility and sustainability in service provision (i.e. through remote delivery) and may support patients to lose weight.

There is an abundance of literature on the use of mobile/digital technology to support weight loss, however the effectiveness of digital interventions to support the delivery of GLP-1 RAs in the community has not been established, in large part due to the recency of these drugs as a treatment option.

The availability of evidence about digital support for other weight loss interventions affords the opportunity to establish factors related to delivery which are commonly associated with successful outcomes. In turn, this can inform the development of digital tools to support the delivery of GLP-1 RAs or GLP-1RA/GIP agonists in the community.

Using the combined approaches of intervention component analysis and component network meta-analysis will allow us to draw out categories of digital components used to support weight loss interventions, and to establish which are most likely to be associated with successful outcomes. This will provide information to help inform the development of future digital support packages for weight loss interventions, specifically the delivery of weight loss drugs.

Overall aim and objective

To identify components of digital support for weight loss interventions that are most likely to be effective in supporting patients to achieve weight loss goals.

Research questions

1) What is the evidence for the effectiveness of weight loss interventions which include digital components?

2) How do we categorise the nature and content of the digital components of included interventions?
3) What is the relative effectiveness of different digital intervention components for weight loss?
4) (exploratory) are there any interactions between digital intervention components?

Methods

We will seek to identify randomised controlled trials of weight loss interventions with digital components. The search will include both free text and controlled vocabulary (eg. MeSH) when available and relevant with no date limit. We will use the Cochrane RCT filter/hedge[8], modified as necessary, and search terms agreed with the project team, with input from PERSPEX, our patient and public engagement group. References will be downloaded into Endnote and de-duplicated.

Information sources

The following databases will be searched from inception to present:

- MEDLINE (Ovid)
- APA PsycINFO (Ovid)
- Embase (Ovid)
- CENTRAL (Cochrane Library)

Ovid MEDLINE(R) ALL <1946 to September 20, 2023>

1 randomized controlled trial.pt.

2 controlled clinical trial.pt.

3 randomized.ab.

4 placebo.ab.

5 drug therapy.fs.

6 randomly.ab.

7 trial.ab.

8 groups.ab.

9 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8

10 exp animals/ not humans.sh.

11 9 not 10

12 Weight Loss/

13 exp Obesity/

14 exp Overweight/

15 Overweight.tw.

16 obes*.tw.

17 (Weight adj2 (over or loss* or gain* or increas* or decreas* or management or control* or reduc* or change*)).tw.

18 ((body mass index or bmi) adj2 (loss* or gain* or increas* or decreas* or control* or reduc* or change*)).tw.

19 12 or 13 or 14 or 15 or 16 or 17 or 18

20 exp Digital Technology/

21 exp Mobile Applications/

22 digital or digitally).tw.

23 (web or mobile or online or app or apps or internet or browser or virtual*).ti.

24 (smartphone* or (smart adj phone*)).tw.

25 ((web* or online) adj support).tw.

26 (mobile adj (device* or health or phone*)).tw.

27 exp Text Messaging/

28 text messag*.tw.

29 (e-health or ehealth or m-health or mhealth).tw.

30 (SMS or MMS).tw.

31 wearable*.tw.

32 (facebook or twitter or snapchat or facetime or Tiktok or youtube or whatsapp or instagram).tw.

33 fitbit.tw.

34 internet.ti.

35 web-based.tw.

36 exp Wearable Electronic Devices/

37 (smart adj (device* or tech*)).tw.

38 (social adj (media or network*)).tw.

39 ((mobile or online or tablet or computer or phone) adj2 (app or apps)).ab.

40 ((web or online or internet or virtual*) adj2 support*).ab.

41 (activity adj2 (tracker* or monitor*)).tw.

42 (Accelerometer* or Pedometer*).ab.

43 (Zoom or skype or "video conferenc*").tw.

44 (support adj2 email*).ab.

45 Smartphone/ or Cell Phone/

46 cell phone*.ab.

47 (reddit or blog or blogs or blogging or webinar* or podcast*).tw.

48 or/20-47

49 11 and 19 and 48

50 exp Artificial Intelligence/

51 "artificial intelligence".tw.

52 chatGPT.tw.

53 50 or 51 or 52

54 48 or 53

55 11 and 19 and 54

56 55 not 49

57 (weight or obes*).ti.

58 56 and 57

59 "virtual diet assistant".kw.

60 chatbot*.ti.

61 57 and 60

Supplementary methods

We will seek additional relevant studies by carrying out citation searching (forward and backwards) of the included papers using Web of Science and Scopus.

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:

Participants must be adults (18 or above) with mean or median BMI of 25 and above, or 23 and above in Asian populations.

Intervention:

Any type of weight loss intervention is eligible, so long as there is a digital component associated with its delivery, and it is delivered not as part of secondary or tertiary care weight loss management. Following the definition adopted by Chan and colleagues[9], we define 'digital' intervention components as follows: interventions that are delivered (either in part or full) via an online platform (e.g. websites, web applications, online forums); a computer or smartphone-based platform (e.g. mobile apps, short message service (SMS)-based interventions, games); or an electronic device of any type.

Interventions solely defined as telemedicine or telehealth, such as phone calls with a clinician or a researcher, will be excluded.

Comparator(s)/control:

Any comparator

Outcomes

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

Study design

Randomised controlled trials

Date limit

No limit

Geographical Context

No restrictions

Language

Articles not written in English will be coded and options for translation considered

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.

Critical appraisal

Risk of bias will be assessed with the Cochrane Risk of Bias tool.

Data Extraction

Key information will be extracted from included trials. 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
- Sample characteristics (sample size, age, % female, BMI, ethnicity, relevant comorbidities etc)
- PROGRESS Plus characteristics
- Weight loss intervention details (name, type, duration, key components etc)
- Comparator details (name, type, duration, key components etc)
- Digital components (name, type, frequency, key components etc)
- Outcomes (all included outcomes)
- Details of weight loss outcome (how evaluated/calculated, time points etc)
- Findings relating to weight loss

Additional data extraction and coding is described in the synthesis section.

Synthesis

Initially, descriptive characteristics of included studies will be tabulated. Further inductive, iterative, cyclical analysis will be performed, in the form of Intervention Component Analysis[10](ICA). ICA is a method of describing and categorising intervention components, appropriate in situations where an existing framework of intervention mechanisms is not applicable.

The process of ICA will involve the following key stages:

- Two reviewers will select a sample of diverse interventions from the included papers and independently extract and categorise key components, using an 'open coding' focusing on breadth in the first instance.
- The reviewers will meet to compare and combine their component lists, identifying a tentative set of codes.
- Using axial coding, that is, to consider relationships between identified components, the reviewers then independently code the remaining interventions.
- The reviewers will meet at regular intervals to compare categories, adding or collapsing them as necessary. Further meetings with review team and members of the PERSPEX PPI groups will take place to sense-check axial coding and overall categories.
- A final list of intervention component descriptors will be produced, using findings from axial coding to organise codes hierarchically (e.g. peer support, with axial codes relating to Facebook, chat function, etc).
- Finally, all trial arms in included studies will be coded using the intervention component descriptors.

Through this cyclical, iterative process, we will be able to identify digital intervention components associated with successful weight loss outcomes. All identified interventions will be eligible for inclusion in the ICA.

Network meta-analysis

We will consider effectiveness on weight loss outcomes over prespecified time frames using random effects component network meta-analysis in a frequentist paradigm. In the first instance, we will use higher-order component codes in an additive model, considering model fit using a deviance test. If the data structure is rich enough, we will consider two-way interactions between components as well. We will only consider trials with a minimum follow-up of 6 months.

PPIE

The project will be discussed with members of the PERSPEX engagement group at monthly intervals throughout the review, from prior to drafting the protocol, through to dissemination. PPIE input will particularly inform:

- Protocol development (including digital interventions of interest)
- ICA coding
- Discussion and interpretation of findings, including perceived omissions in the evidence
- Dissemination strategy

Dissemination and timeline

A NIHR report will be produced in the first instance. Findings will also be prepared for journal article submission, and presentation at relevant conferences will be considered. Plain English summaries will

be produced and other media outputs (twitter, Canva cards, comic strips, podcasts etc) will be considered.

The review will take approximately 6 months from the date the searches are conducted.

Funding

This review is funded by the NIHR Evidence Synthesis Programme.

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).
4. National Institute for Health and Care Research (NIHR). *Managing obesity in men*. National Institute for Health and Care Research; 2016. URL: https://evidence.nihr.ac.uk/collection/managing-obesity-in-men/ (accessed 9 October 2023; doi: 10.3310/highlight-000844). https://doi.org/doi: 10.3310/highlight-000844
5. NHS Digital. *Statistics on Obesity, Physical Activity and Diet - England, 2017*. London: NHS Digital; 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#resources (accessed 9 October 2023).
6. The Organisation for Economic Co-operation and Development (OECD). *Obesity Update 2017*. OECD; 2017. URL: https://www.oecd.org/els/health-systems/Obesity-Update-2017.pdf (accessed 9 October 2023).
7. National Institute for Health and Care Excellence (NICE). *NICE committee recommends tirzepatide as new treatment option for people with type 2 diabetes*. National Institute for Health and Care Excellence; 2023. URL: https://www.nice.org.uk/news/article/nice-committee-recommends-tirzepatide-as-new-treatment-option-for-people-with-type-2-diabetes (accessed 2 November 2023).
8. Lefebvre C, Glanville J, Briscoe S, Featherstone R, Littlewood A, Marshall C*, et al. Chapter 4: Searching for and selecting studies. Cochrane Handbook for Systematic Reviews of Interventions version 6.3 (updated February 2022).* Cochrane; 2022. URL: https://training.cochrane.org/handbook/current/chapter-04#_Ref535510197 (accessed 9 October 2023).
9. Chan A, De Simoni A, Wileman V, Holliday L, Newby CJ, Chisari C*, et al.* Digital interventions to improve adherence to maintenance medication in asthma. *Cochrane Database Syst Rev* 2022;**6**:Cd013030. https://doi.org/10.1002/14651858.CD013030.pub2
10. Sutcliffe K, Thomas J, Stokes G, Hinds K, Bangpan M. Intervention Component Analysis (ICA): a pragmatic approach for identifying the critical features of complex interventions. *Syst Rev* 2015;**4**:140. https://doi.org/10.1186/s13643-015-0126-z