



# Association of Glucagon-like Peptide 1 Analogs and Agonists Administered for Obesity with Weight Loss and Adverse Events: A Systematic Review and Network Meta-analysis

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## ARTICLE INFO

### Article History:

Received 31 August 2021

Revised 29 October 2021

Accepted 9 November 2021

Available online xxx

## ABSTRACT

**Background:** Comparative effectiveness of 7 glucagon-like peptide 1 (GLP-1) agents on weight loss (WL) in obesity remains unknown.

**Methods:** We performed a systematic review, network meta-analysis (NMA) utilizing the following data sources: MEDLINE, EMBASE, Scopus, Cochrane Central and clinical trial registries, from inception to March 2, 2021. The prespecified criteria for study inclusion were randomized clinical trials (RCTs) of  $\geq 12$  weeks' duration. The data appraisal and extraction were performed by two investigators independently, using the published reports. The main outcomes and statistical methods were weight loss over placebo (WLOP) and adverse events (AEs) among GLP-1 agents using random-effects NMA (frequentist approach); relative ranking using surface under the cumulative ranking (SUCRA) method and certainty of evidence using grading of recommendations, assessment, development and evaluations (GRADE).

**Findings:** 64 RCTs (from 2004 to 2021) included 27018 patients (median of age, 55.1 years old; 57.4% women; baseline weight 94.8kg and BMI 33.0kg/m<sup>2</sup>; trial duration 26 weeks). Direct meta-analysis showed significant WLOP with: -1.44kg (95% CI, -2.14 to -0.74) with dulaglutide  $\geq 1.5$  mg; -1.82kg (-2.42 to -1.23) with exenatide immediate release (IR); -2.20kg (-4.31 to -0.08) with exenatide extended release (ER); -3.20kg (-6.53 to 0.15) with efglenatide; -2.72kg (-3.35 to -2.09) with liraglutide  $\leq 1.8$ mg; -4.49kg (-5.26 to -3.72) with liraglutide  $> 1.8$ mg; -0.62kg (-1.22 to -0.02) with lixisenatide; -4.33kg (-5.71 to -3.00) with semaglutide SQ  $< 2.4$ mg; -9.88kg (-13.17 to -6.59) with semaglutide SQ 2.4mg; -2.73kg (-4.81 to -0.65) with semaglutide oral; and -1.71kg (-2.64 to -0.78) with taspoglutide. Highest WLOP were with semaglutide SQ 2.4mg and  $< 2.4$ mg, and liraglutide  $> 1.8$ mg (SUCRAs 100, 86.1, 82.8 respectively). Highest SUCRAs for discontinuation due to AEs were with taspoglutide and liraglutide  $> 1.8$ mg. Risk of bias was high or unclear for random sequence generation (29.7%), allocation concealment (26.6%), and incomplete outcome data (26.6%). Heterogeneity ( $I^2 > 50\%$ ) in WL and AEs reflected magnitude, not direction of effect.

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## 1. Introduction

It is estimated that about 1.9 billion adults are overweight and 600 million have obesity worldwide [1]. Obesity increases the risk of type 2 diabetes and cardiovascular disease, in part related to genetic and lifestyle-related causes [2] leading to high health-care costs

attributable to obesity-related diseases [3]. Prior systematic reviews have documented the relative efficacy of different classes of obesity medications, including glucagon-like peptide-1 (GLP-1) analogs and agonists, on weight loss and cardiometabolic health.[4,5] The odds of discontinuation of therapy due to medication-related adverse events were not different for phentermine-topiramate, liraglutide, and naltrexone-bupropion [4]. The magnitude of weight loss relative to placebo treatment achieved with the GLP-1 analog, liraglutide, was greater than that observed with lorcaserin and orlistat, similar to naltrexone-bupropion, and slightly lower than that observed in two

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## Research in context

### *Evidence before this study*

Prior systematic reviews and meta-analyses have documented the effects of diverse pharmacological treatments for obesity on weight loss, cardiometabolic risk factors, and adverse effects. The most efficacious class of pharmacological treatments are the GLP-1 agonists or analogs. However, the relative efficacy of the latter agents remains unclear.

### *Added value of this study*

The current study, based on 64 randomized, controlled trials (2004–2021) and 27018 patients, provides an estimate of the relative efficacy of the available GLP-1 agonists or analogs, as well as the risk of adverse effects. The network meta-analysis suggests that the greatest efficacy is observed with liraglutide and semaglutide.

### *Implications of all the available evidence*

This analysis, as well as future studies replicating these findings, may inform clinical practice as well as guidelines and policies with regards to pharmacological treatment of obesity.

trials with phentermine-topiramate [4]. This observation and the multiple GLP-1 agents tested or available for prescription provided the rationale for the current study of the relative efficacy of the diverse GLP-1 agents.

The metabolic effects of GLP-1 agonists and analogs reflect the effects described for endogenous GLP-1 on peripheral and central mechanisms involved in weight control such as appetite, food intake, and glycemic control. The peripheral actions include activation of the ileal brake, delay in gastric emptying, increase in glucose-dependent insulin release, decrease in glucagon secretion, and increase in pancreatic  $\beta$  cell growth. [6,7] GLP-1 and GLP-1 agonists or analogs also reduce appetite through effects on several regions of the human central nervous system that express GLP-1 receptors including the parietal and orbitofrontal cortex, hypothalamus, [8] and medulla (such as the nucleus of solitary tract); for example, the GLP-1 analog, liraglutide, alters brain activity related to highly desirable food cues [9–13]. Retardation of gastric emptying is partly impacted by tachyphylaxis, but upper gastrointestinal symptoms such as nausea or vomiting may lead to discontinuation, sometimes affecting 6 to 16% of participants in randomized clinical trials (RCTs) of liraglutide [14–17]. In an earlier analysis, discontinuations with GLP-1 agents were reported as exenatide and liraglutide 1.2mg (both 19%), and liraglutide 1.8mg (16%) [18]. The US Food and Drug Administration (FDA) has approved liraglutide 3.0mg and subcutaneous (SQ) semaglutide 2.4mg for weight loss, and several GLP-1 analogs or agonists in diverse formulations or doses for the treatment of type 2 diabetes mellitus: dulaglutide, exenatide [immediate release (IR) and extended release (ER)], efpeglenatide, liraglutide, lixisenatide, semaglutide (SQ and oral), and tasoglutide.

However, there is a paucity of RCT evidence comparing the efficacy and adverse effects of the different GLP-1 agonist or analog treatments with each other. It is relevant that data regarding relative efficacy and adverse effects of each drug can inform patients, health care practitioners, and policymakers regarding the optimal GLP-1 medication prescription to treat obesity and overweight. The objective of this systematic review and network meta-analysis was to compare the associations of each GLP-1 agonist or analog with weight loss and adverse effects using a direct meta-analysis and random-effects network meta-analysis using a frequentist approach.

## 2. Methods

We conducted a systematic review and network meta-analysis. The meta-analysis was conducted following principles described in the Cochrane Handbook for Systematic Reviews of Interventions [19]. Pairwise random-effect meta-analysis was performed by synthesizing data from trials comparing at least one GLP-1 agonist or analog drug with placebo. Network meta-analysis was conducted to compare different drugs and doses. Results were reported according to PRISMA Extension Statement for Reporting of Systematic Incorporating Network Meta-analyses of Health Care Interventions [20]. Certainty of evidence was assessed using Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach for network meta-analysis [21].

## 3. Criteria for study inclusion

We included parallel, randomized clinical trials which studied one or more GLP-1 agonist or analog drug compared to placebo treatment for at least 12 weeks (a recognized minimum duration in the application of pharmacotherapy for obesity for achieving meaningful and, for many medications, near-maximal weight loss), and at least 12 weeks of follow-up. The included studies were conducted in adults (>18 years) with obesity or overweight [body mass index (BMI) >25 kg/m<sup>2</sup>] in White, Hispanic, and Black individuals, and BMI >23kg/m<sup>2</sup> in Asian populations] and documented the measured change in mean weight.

Patients with or without diabetes mellitus or nonalcoholic fatty liver disease (NAFLD) were included. We excluded open-labeled, cross-over design, or non-placebo-controlled trials (e.g., trials with active or no intervention comparators), as well as trials in specific populations such as patients with polycystic ovary syndrome. There was no language limitation.

## 4. Data sources and searches

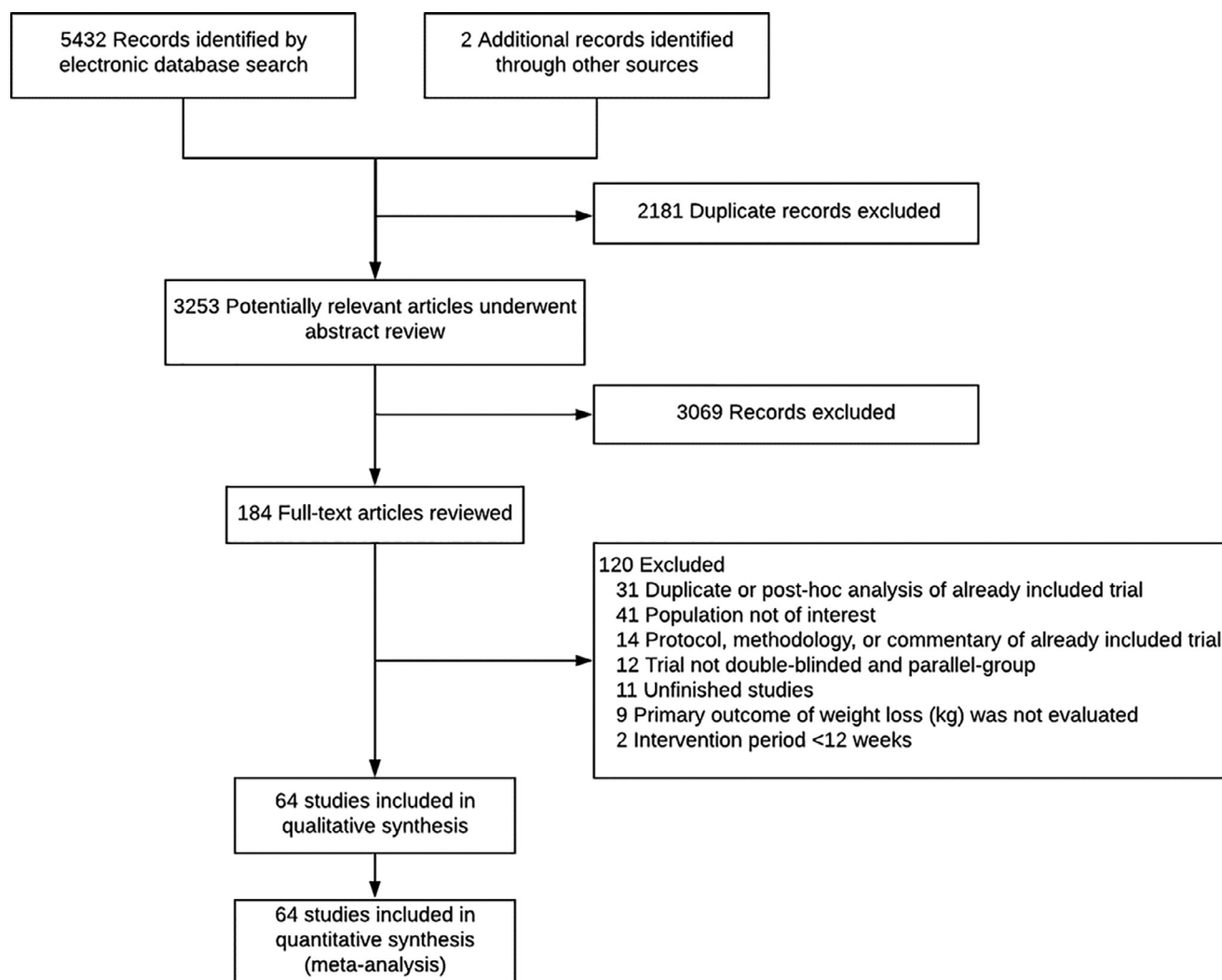
A medical librarian (LJP) developed and conducted the search strategy (**see eMethods in Supplemental Material**) using inputs from the study investigators. The search included Ovid MEDLINE, Cochrane Central Register of Controlled Trials, EMBASE, clinical trial registries and Scopus from inception to March 2, 2021. A repeat literature search conducted on October 10, 2021 revealed no relevant additional clinical trials pertaining exclusively to this class of GLP-1 agents. Published review articles and content experts were used to identify relevant articles missed by the electronic search. The data sought included individual patient data. We did not seek data from any unpublished studies. Details of the electronic search strategy are presented in **eMethods** in Supplemental Material.

## 5. Study selection

Two investigators (KV and KK) independently screened the titles and abstracts to select potentially eligible studies based on prespecified eligibility criteria. Discrepancies were discussed until a consensus was reached. Any potentially relevant citation was then retrieved in full-text and reviewed by the same two investigators to evaluate the inclusion/exclusion criteria and to determine inclusion. Discrepancies were resolved through discussion with a third investigator (MC). Excluded studies at this step were listed with the reason for exclusion.

## 6. Data extraction and quality assessment

Two investigators (JA and LK) independently reviewed the main reports and supplementary materials, including data reported in the ClinicalTrials.gov portal, and extracted trial and patient



**Figure 1.** Flow chart summarizing study retrieval and identification

characteristics, duration of treatment strategies, and outcomes using a predesigned form in order to prepare the data for synthesis. Discrepancies were resolved by referring to the original article in consultation with a third investigator (MC).

Details of the extracted variables are presented in **eTable 1** in the Supplemental Material. The data extraction form is included in **eFigure 1** in the Supplemental Material. Active durations of treatments of each trial were classified into one of the following drug-dosage combinations: dulaglutide <1.5mg, dulaglutide  $\geq$ 1.5mg, exenatide IR, exenatide ER, efpeglenatide, liraglutide  $\leq$ 1.8mg, liraglutide >1.8mg, lixisenatide, semaglutide SQ <2.4mg, semaglutide SQ 2.4mg, semaglutide oral, and taspoglutide. In trials where participants were randomized to different dosages of a GLP-1 agonist or analog, the intervention arms with different dosages were pooled and classified into the pertinent drug-dosage category.

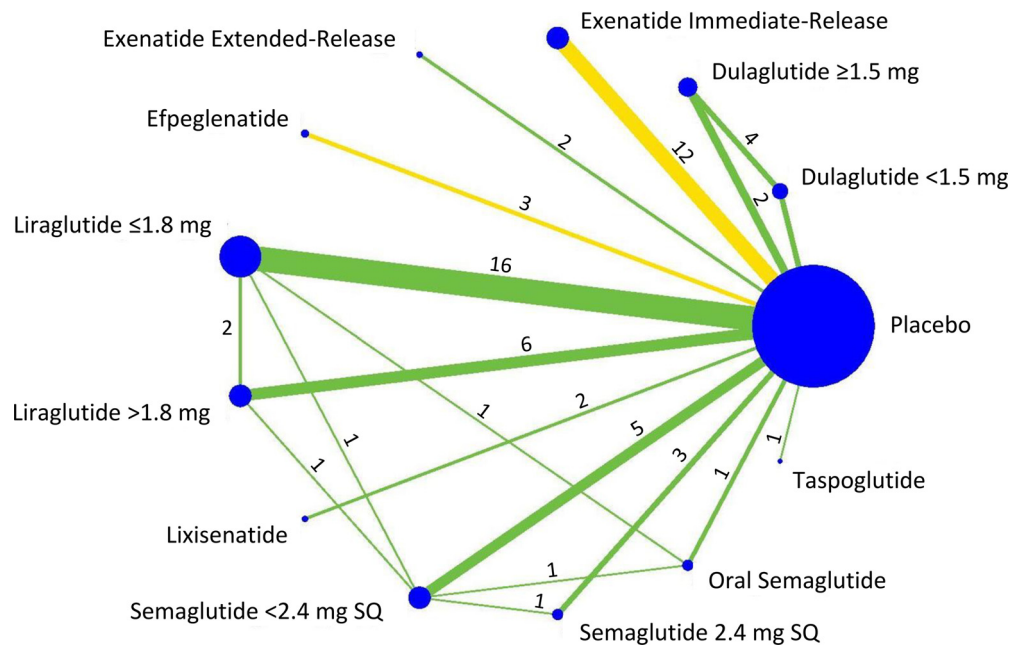
The primary outcome was to assess the effect of GLP-1 agonists or analogs on change in weight compared to placebo in adults with obesity or overweight. The primary safety outcome was the rate of individuals with adverse events leading to discontinuation of trial treatment. Secondary safety outcomes were rates of participants with nausea, vomiting, and serious adverse events.

Two reviewers (JA and LK) assessed the study risk of bias using the Cochrane Risk of Bias assessment tool [22]. Certainty in the pooled estimates was assessed using the GRADE approach for network meta-analysis [21]. In this approach, investigators rate the certainty of evidence separately for direct, indirect, and NMA

(combined direct + indirect) estimates. Certainty in direct estimates obtained from head-to-head comparisons starts as high and can be downgraded to moderate, low, and very low based on risk of bias, indirectness, imprecision, inconsistency (or heterogeneity), and publication bias. This was followed by rating of the indirect estimates, which starts at the lowest rating of the two pairwise estimates that contribute as first-order loops to the indirect estimate without considering imprecision. Intransitivity (significant differences between the characteristics of the studies in the first-order loop) was considered a reason to lower certainty in the indirect estimate. Finally, certainty of NMA estimate was defined as the highest rating between direct and indirect evidence of a given comparison, if the direct and indirect estimates were similar (i.e., coherent), and after applying the rules of imprecision to the NMA estimate. If the direct and indirect estimates were incoherent, we rated down the NMA estimate for incoherence. Alternatively, the direct estimates were used as the best evidence.

## 7. Outcomes, data synthesis and analysis

The primary outcomes extracted were weight loss and adverse effects, in particular discontinuation due to adverse effects. The analysis performed to assess discontinuations did not adjust for differences in dose escalation regimens across the RCTs which ranged from inflexible (subjects exit if unable to tolerate the medication) to flexible dose escalation protocols with ability to decrease the dose or



**Figure 2.** Network of included trials and available direct comparisons for weight loss. Color of the comparison lines shows the average estimated risk of bias for each direct comparison: green reflects low risk and yellow reflects unclear risk of bias. Numbers above lines indicate numbers of trials for each comparison.

maintain a given dose for a longer period of time before escalating to the next dose level to enable retention in the study on treatment.

Treatment effects and 95% confidence intervals were estimated by pairwise meta-analysis using DerSimonian and Laird random-effects model [23]. The effects of treatment compared to placebo were estimated using mean difference (MD) for weight loss and relative risk (RR) for adverse events leading to discontinuation, nausea, vomiting, and serious adverse events (together with 95% confidence interval).

I<sup>2</sup> statistics was used to quantify the degree of heterogeneity (variability within studies of each of the GLP-1 agents) with values over 50%, indicating substantial heterogeneity [24]. Publication bias was assessed by examining funnel plot asymmetry using the linear regression method of Egger's test [25].

To integrate indirect and direct estimates, random-effects network meta-analysis was performed using a frequentist approach. Relative ranking of agents was assessed using surface under the cumulative ranking (SUCRA) method. Higher SUCRA scores reflect higher probability of being most effective in terms of weight loss and lower likelihood of adverse events. The analysis was conducted using the network suite [26,27] in STATA (StataCorp. 2019. *Stata Statistical Software: Release 16*. College Station, TX: StataCorp LLC.).

## 8. Role of the funding source

There was no funding used to conduct this study other than support of research time for the PI's research program on a GLP-1 agent in obesity from NIH R01-DK67071. The funding source had no access to data and was not involved in the decision to submit for publication. All of the authors had access to the data and decided to submit the manuscript for publication.

## 9. Results

The search strategy retrieved 3253 unique references from RCTs. Of these references, 64 RCTs fulfilled the inclusion criteria (Figure 1). The data extracted from the included randomized clinical trials are shown in eTable 1 in Supplemental Material; the characteristics of included randomized clinical trial including route, dose, and frequency of medications, duration of trial, study population as well as

the total number of participants randomized, included in the weight or BMI analysis, completers, and attrition rate are summarized in eTable 2 in Supplemental Material. The baseline patient characteristics in the included randomized controlled trials with each GLP-1 agent are summarized in eTable 3 in Supplemental Material.

After classification of the active durations of treatments based on the predefined drug-dosage combinations, 53 of these RCTs provided two-group comparisons consisting of a placebo group and one drug-dosage group (dulaglutide  $\geq 1.5$ mg, 2 trials; [28,29] exenatide IR, 12 trials; [30–41] exenatide ER, 2 trials; [42,43] efgpeglenatide, 3 trials; [44–46] liraglutide  $\leq 1.8$ mg, 16 trials; [47–62] liraglutide  $> 1.8$ mg, 6 trials; [17,63–67] lixisenatide, 2 trials; [68,69] semaglutide SQ  $< 2.4$ mg, 5 trials; [70–74] semaglutide SQ 2.4mg, 3 trials; [75–77] semaglutide oral, 1 trial; [78] and taspoglutide, 1 trial [79]). In addition, 11 studies provided three-group comparisons consisting of one placebo group and two drug-dosage groups (dulaglutide  $< 1.5$ mg and dulaglutide  $\geq 1.5$ mg, 4 trials; [80–83] liraglutide  $\leq 1.8$ mg and liraglutide  $> 1.8$ mg, 2 trials; [84,85] liraglutide  $\leq 1.8$ mg and semaglutide SQ  $< 2.4$ mg, 1 trial; [86] semaglutide SQ  $< 2.4$ mg and semaglutide oral, 1 trial; [87] liraglutide  $> 1.8$ mg and semaglutide SQ  $< 2.4$ mg, 1 trial; [88] semaglutide SQ  $< 2.4$ mg and semaglutide SQ 2.4mg, 1 trial; [89] and liraglutide  $\leq 1.8$ mg and semaglutide oral, 1 trial [90]). A network of direct comparisons is presented in Figure 2.

## 10. Trial and participant characteristics and risk of bias

Overall, 64 RCTs reported between 2004 and 2021 and involving 27018 participants were included. In three of these RCTs (2629 participants), two different GLP-1 agonists or analogs were tested vs. placebo. The number of participants randomized to active treatments ranged from 11<sup>40</sup> to 2487<sup>66</sup> [median, 196 (IQR, 35–322)]. The attrition rate was generally comparable between the active and placebo treatment groups, and ranged from 0% to 47% [median, 11% (IQR, 5.5–17%)] in active treatment groups and from 0% to 56% [median, 11% (IQR, 6–18.5%)] in placebo groups.

The duration of treatments ranged from 12 to 160 weeks, with a median of 26 weeks (IQR, 20–30 weeks). Four studies administered a glucose lowering drug as a co-treatment to all participants in the placebo and active treatment groups (metformin, 3 studies; [53,54,82]



**Table 1**

Estimates of pairwise meta-analyses for excess weight loss and adverse events vs. placebo (I=immediate; E= extended; AE= adverse event).

GLP-1 agents and dosage	Weight loss vs. placebo		Discontinuation of GLP-1 agonist/analog due to AE		No. of patients with nausea		No. of patients with vomiting	
	No. of Trials	Weighted mean difference, kg (95% CI)	No. of trials	Relative risk (95% CI)	No. of trials	Relative risk (95% CI)	No. of trials	Relative risk (95% CI)
Dulaglutide <1.5 mg	4	-0.48 (-1.24 to 0.28)	4	0.50 (0.16 to 1.52)	4	1.42 (0.72 to 2.78)	4	0.99 (0.27 to 3.72)
Dulaglutide ≥1.5 mg	6	-1.44 (-2.14 to -0.74)	6	4.14 (1.66 to 10.33)	6	2.71 (1.47 to 5.00)	5	2.76 (1.42 to 5.38)
Exenatide I Release	12	-1.82 (-2.42 to -1.23)	12	2.01 (1.36 to 2.96)	9	2.58 (1.70 to 3.91)	9	3.73 (2.65 to 5.26)
Exenatide E Release	2	-2.20 (-4.31 to -0.08)	2	0.29 (0.03 to 3.25)	1	1.36 (0.33 to 5.62)	1	0.41 (0.01 to 19.4)
Efpeglenatide	3	-3.20 (-6.53 to 0.15)	3	2.49 (1.06 to 5.86)	3	3.02 (1.06 to 8.64)	3	3.91 (1.81 to 8.45)
Liraglutide ≤1.8mg	20	-2.72 (-3.35 to -2.09)	20	2.12 (1.44 to 3.12)	13	3.07 (1.99 to 4.72)	11	2.33 (1.59 to 3.41)
Liraglutide > 1.8mg	9	-4.49 (-5.26 to -3.72)	9	2.32 (1.49 to 3.63)	7	2.62 (2.37 to 2.90)	6	3.62 (2.88 to 4.55)
Lixisenatide	2	-0.62 (-1.22 to -0.02)	2	1.74 (0.86 to 3.51)	2	3.82 (1.24 to 11.75)	2	4.35 (0.07 to 256.65)
Semaglutide <2.4mg	9	-4.33 (-5.71 to -3.00)	9	2.56 (1.44 to 4.58)	9	3.47 (2.73 to 4.41)	9	5.08 (3.30 to 7.81)
Semaglutide 2.4mg	4	-9.88 (-13.17 to -6.59)	4	1.98 (1.32 to 2.98)	4	2.65 (2.30 to 3.04)	4	3.41 (2.59 to 4.49)
Semaglutide oral	3	-2.73 (-4.81 to -0.65)	3	2.55 (1.24 to 5.24)	3	5.41 (2.14 to 13.65)	3	2.72 (1.07 to 6.93)
Taspoglutide	1	-1.71 (-2.64 to -0.78)	1	3.87 (1.44 to 10.35)	0	N/A	0	N/A
Total # of trials (# of comparisons)	64 (75)	-3.11 (-3.64 to -2.57)	64 (75)	2.17 (1.85 to 2.56)	48 (61)	2.75 (2.44 to 3.09)	46 (57)	3.22 (2.74 to 3.78)

and dapagliflozin, 1 trial [43]). Two RCTs did not allow any glucose lowering medications alongside the trial treatment, including one trial which recruited only treatment-naïve participants [35] and one trial which excluded any patients who received anti-diabetes medications within 90 days before screening [78]. The rest of the trials allowed at least one glucose or weight lowering agent alongside the trial treatment. Details of the RCTs included in this meta-analysis are summarized in **eTable 2** in the Supplemental Material.

Overall, 57.4% of the participants were female (range, 19.8%–81.5%) and 74.9% were of white race (range 36.6%–100%). The median of the mean age at randomization was 55.1 years (range, 37–65.8 years). At randomization, the median of mean weight was 94.3kg (IQR, 90.5–100kg) in placebo groups and 95.3kg (IQR, 92.1–100.5kg) in active treatment groups, and the median of mean BMI was 32.9kg/m<sup>2</sup> (IQR, 31.9–35kg/m<sup>2</sup>) in placebo groups and 33.1kg/m<sup>2</sup> (IQR, 32–34.4kg/m<sup>2</sup>) in active treatment groups. **eTable 3** in the Supplemental Material presents details of patient characteristics in the included RCTs.

Overall, the risk of bias was high or unclear for random sequence generation in 19 trials (29.7%), allocation concealment in 17 trials (26.6%), and incomplete outcome data in 17 trials (26.6%). Blinding of participants and personnel, blinding of outcome assessment, and possibility of selective reporting were adequate in all trials. Study level and overall risk of bias assessments are summarized in **eFigure 2** in the Supplemental Material.

## 11. Primary assessments

### 11.1. Pairwise direct meta-analysis

The results of treatment effects and adverse events estimates of GLP-1 agonists or analogs compared to placebo in pairwise meta-analyses are shown in **Table 1**. Overall, all drug-dosage groups combined, and GLP-1 agonists or analogs showed excess weight loss of 3.11kg (95% CI, -3.64 to -2.57) compared to placebo. All drug-dosage categories except dulaglutide <1.5mg and efpeglenatide (all doses) were associated with significant excess weight loss compared to placebo. The excess weight losses compared to placebo (see Forest plot in **eFigure 3** in the Supplemental Material) are detailed in **Table 1**.

All drug-dosage groups were associated with a significantly higher rate of medication discontinuation due to adverse events except dulaglutide <1.5mg with a relative risk (RR) of 0.5 (95% CI, 0.16 to 1.52); exenatide ER with an RR of 0.29 (95% CI, 0.03 to 3.25); and lixisenatide with an RR of 1.74 (95% CI, 0.86 to 3.51) (see Forest plot in **eFigure 4** in the Supplemental Material). Overall, GLP-1 agonists or analogs (all drug-dosages combined) increased the number

of patients with nausea [RR, 2.75 (95% CI, 2.44 to 3.09)] and vomiting [RR, 3.22 (95% CI, 2.74 to 3.78)] compared to placebo.

Substantial heterogeneity ( $I^2 > 50\%$ ) was observed for most of the weight loss and adverse events comparisons. Variations, however, were mostly in the magnitude of effect, not in the direction of effect.

### 11.2. Comparison of efficacy of GLP-1 agents in only diabetic or only non-diabetic participants

**eTable 4** in the Supplemental Material shows the pairwise analysis for excess weight loss over placebo in all studies, and separately for studies performed only in diabetic or non-diabetic participants. Two of the 67 studies were excluded from this analysis because they enrolled both diabetic and non-diabetic participants. Both groups of participants (weighted mean difference of -3.11 [95% CI -3.64 to -2.57] kg overall, -2.19 [95% CI -2.56 to -1.83] kg in diabetic and -6.09 [95% CI -7.62 to -4.57] kg in non-diabetic participants) had significant overall effects on excess weight loss over placebo. In addition, meta-regression model showed that, after adjustment for drug/dosage group, being non-diabetic was associated with excess weight loss with a coefficient of -2.62 (95% CI, -3.82 to -1.42) kg ( $p < 0.001$ ).

Forest plots of the excess weight losses compared to placebo for the studies focused on diabetic participants and non-diabetic participants are included in Supplemental Material **eFigures 5** and **6**.

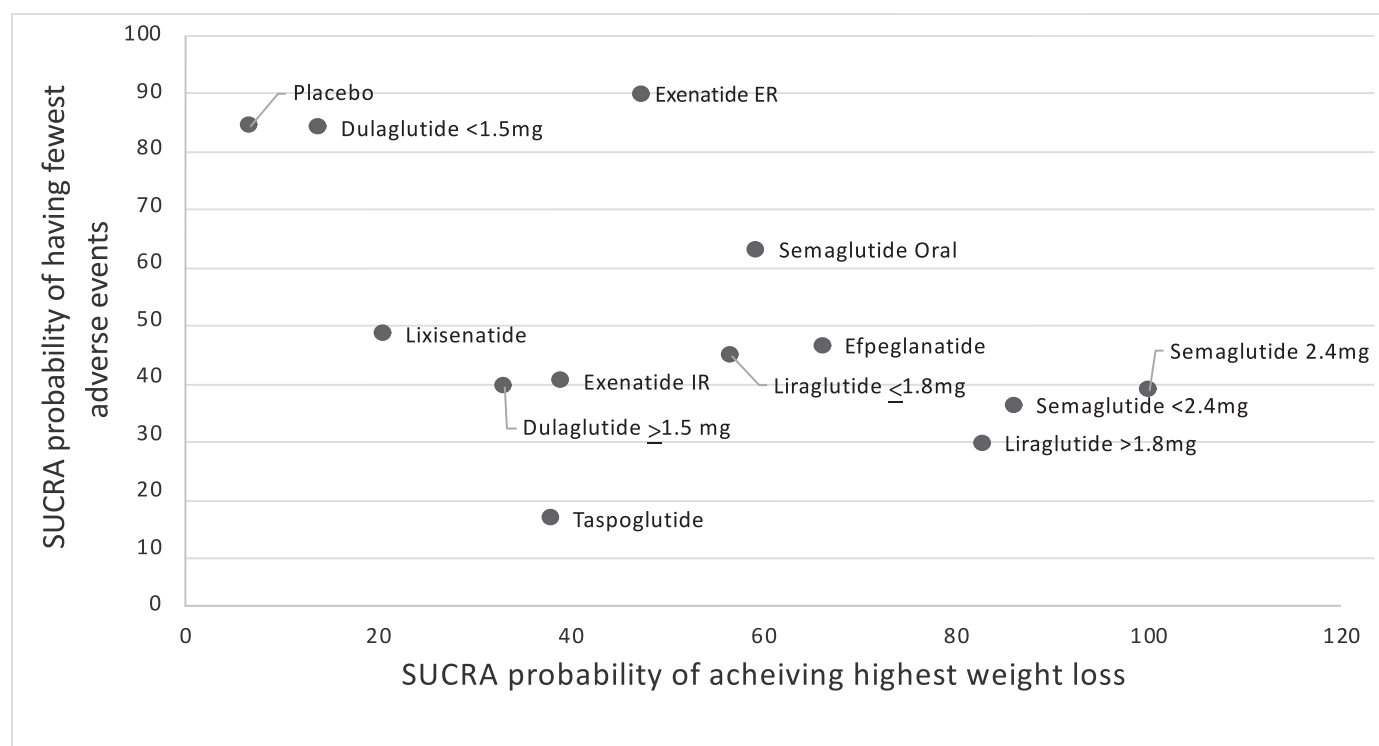
### 11.3. Network meta-analysis

#### 11.3.1. Excess weight loss compared with placebo

In network meta-analysis compared with placebo, the following were associated with significant excess weight loss: dulaglutide ≥1.5mg, exenatide IR, liraglutide ≤1.8mg, liraglutide > 1.8mg, semaglutide SQ <2.4mg, semaglutide SQ 2.4mg, and semaglutide oral. The following did not show a statistically significant excess weight loss in comparison with placebo: dulaglutide <1.5mg, exenatide ER, lixisenatide; and taspoglutide. Network meta-analysis showed that semaglutide SQ 2.4mg was associated with excess weight loss compared to all other active agents (**Table 2**). SUCRA-based treatment ranking suggested that semaglutide SQ 2.4mg (SUCRA, 100) was most likely to result in the highest excess weight loss, followed by semaglutide <2.4mg (SUCRA, 86.1), liraglutide > 1.8mg (SUCRA, 82.8), efpeglenatide (SUCRA, 66.2), semaglutide oral (SUCRA, 59.4), liraglutide ≤1.8mg (SUCRA, 58), exenatide ER (SUCRA, 56.7), exenatide IR (SUCRA, 39.1), taspoglutide (SUCRA, 38), dulaglutide ≥1.5mg (SUCRA, 33.2), lixisenatide (SUCRA, 20.6), and dulaglutide <1.5mg (SUCRA, 13.9) (**Figure 3** and see Forest plots in **eFigure 7** for SUCRA curves for



### Overall efficacy balancing probabilities of achieving highest weight loss relative to probability of experiencing adverse events (SUCRA: surface under the cumulative ranking )



**Figure 3.** Overall efficacy balancing probabilities of achieving highest weight loss relative to probability of experiencing adverse events

conduct of the RCTs compared to placebo, with the highest odds ratios for taspoglutide and liraglutide >1.8mg. Frequently encountered symptoms were nausea and vomiting. By SUCRA probabilities, the GLP-1 agonists or analogs least likely to be associated with discontinuation because of adverse events were exenatide ER and dulaglutide <1.5 mg.

Our study has suggested the relative efficacy of all available GLP-1 agents for weight loss. This is the first systematic review and network meta-analysis of the 7 different agents in this category, and it enhances the previously published systematic reviews and meta-analyses of pharmacological treatments for obesity and their effects on weight loss as well as cardio- metabolic factors [4,5].

In recommendations on prevention of obesity-related morbidity and mortality in adults, [92] the US Preventive Services Task Force (USPSTF) recommended multi-component treatments including pharmacological therapies and surgical weight loss procedures. The current study expands on the insights included in the USPSTF document of 2018 [93] which summarized pharmacotherapy trials that evaluated liraglutide (4 trials), lorcaserin (4 trials), naltrexone and bupropion (3 trials), orlistat (21 trials), and phentermine-topiramate (3 trials) in combination with behavioral counseling. In addition, [4] a systematic review and meta-analysis of the broader spectrum of drugs included in the USPSTF recommendation found moderate-quality evidence for phentermine-topiramate being associated with higher odds of achieving predefined thresholds of clinically meaningful weight loss compared with other currently approved agents.

In the future, comparison of selective GLP-1 agonists or analogs with dual glucose-stimulated insulinotropic peptide agonist, tirzepatide, will be of significant interest, given a recent report [94] of greater weight loss with 10 and 15 mg SQ tirzepatide weekly in comparison to 1mg SQ semaglutide weekly in patients with type 2 diabetes mellitus. In addition, comparisons with SQ semaglutide doses >2.4mg weekly would be of great interest, given the results showing this was the most effective GLP-1 agent in the current NMA.

There is paucity of direct comparative trials which are needed to confirm indirect comparisons obtained through NMA. On the other hand, the risk of bias in the available trials was judged to be low. Most trials attempted to control for concomitant interventions such as diet, exercise, and behavioral modification, although these were not necessarily measured as potential confounders in appraising the relative efficacy of each of the GLP-1 agents assessed. The fact that the attrition rates in the active treatment arms and placebo groups were similar (median 11%) is nevertheless reassuring that dropout is less likely to lead to important bias in the assessment of efficacy or adverse events. Risk of bias was high or unclear for random sequence generation (29.7%), allocation concealment (26.6%), and incomplete outcome data (26.6%). Heterogeneity ( $I^2 >50\%$ ) in weight loss and adverse events reflected magnitude, not direction of effect.

The strengths of this systematic review and meta-analysis relate to selecting studies by independent pairs and following an a priori established analysis plan. Limitations include that analysis did not correct for quantity of data (i.e., numbers of studies, numbers of enrollees) for different medications, analysis performed to assess discontinuations did not adjust for differences in dose escalation regimens across the RCTs, and racial diversity was not sufficient to ensure that the results and conclusions are generalizable to races other than Caucasians. In addition, there is uncertainty in the strength of conclusions due to the presence of substantial heterogeneity, and some of the medications evaluated are either not yet marketed (efpeglatanide) or are no longer in development (taspoglutide). Future research needs to include direct comparisons between the different agents, particularly semaglutide and liraglutide which appear to demonstrate the greatest efficacy in the current network meta-analysis.

In summary, in our analysis among adults with obesity or overweight, semaglutide (SQ and oral) and liraglutide were the most efficacious GLP-1 agents to induce weight loss over at least 12 weeks of treatment. This analysis, as well as future studies replicating these

findings, may inform clinical practice as well as guidelines and policies with regards to pharmacological treatment of obesity.

### Contributors

K. Vosoughi and J. Atieh: co-first authors of the paper, fellow investigators, literature search

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M.H. Murad: supervisor of all analyses (including SRMA), conduct of network meta-analysis, co-author

M. Camilleri: principal investigator, content expertise, data analysis and principal authorship

### Interpretation

According to our analysis, semaglutide (SQ, oral) and liraglutide (SQ) were the most efficacious GLP-1 agents to induce WL during  $\geq 12$  weeks' treatment.

### Funding

There was no funding used to conduct this study other than support of research time for the PI's research program on a GLP-1 agent in obesity from NIH R01-DK67071.

### Data sharing

There are no new original data in this article, as this is a review of the literature.

### Funding

There was no extramural funding used to conduct this study other than support of research time for the PI's research program on a GLP-1 agent in obesity from NIH R01-DK67071.

### Declaration of Competing Interest

Dr. Camilleri is supported by grant R01-DK67071 from National Institutes of Health for mechanistic studies of obesity including GLP-1 agonists/analogues. Dr. Camilleri serves on an advisory board for Phenomix Sciences regarding the company's development of a test to predict weight loss response to obesity therapy, and he is a stockholder in the company. Phenomix Sciences has obtained an exclusive license to Dr. Camilleri's and a Mayo Clinic co-investigator's biomarker technology, submitted patent, and know-how to develop a biomarker to predict response to obesity pharmacotherapy. Dr. Camilleri also serves as a consultant to Kallyope for the company's development program regarding obesity (the consulting fee is paid to his employer, Mayo Clinic). Dr. Camilleri has a patent application pending regarding obesity metabolomics to identify different phenotypes with the United States Patent and Trademark Office. The other authors have no conflicts of interest.

### Acknowledgements

The authors thank Mrs. Cindy Stanislav for secretarial support.

### Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.eclinm.2021.101213.

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