Obesity Science & Practice

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REVIEW OPEN ACCESS

Role of Oral Glucagon-Like Peptide-1 Receptor Agonists in Weight Management for Individuals With Overweight or Obesity Without Diabetes: A Network Meta-Analysis of Randomized Controlled Trials

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Received: 22 January 2026 | **Revised:** 7 July 2026 | **Accepted:** 29 July 2026

Keywords: danuglipron | obesity | oral GLP-1 RA | oral semaglutide | orforglipron | overweight | weight loss

ABSTRACT

Background: Oral GLP-1 receptor agonists (GLP-1 RAs) offer a non-injectable option for weight management in adults with overweight/obesity without diabetes. This network meta-analysis (NMA) evaluated their effects on body weight.

Methods: A frequentist random-effects NMA of RCTs comparing oral GLP-1 RAs with placebo in adults without diabetes was conducted by searching databases through 30 April 2026. The primary outcome was percent change in body weight, with secondary outcomes including other weight measures and weight thresholds. Analyses used R (netmeta), and certainty was assessed with CINeMA.

Results: Nine RCTs (N = 5766; 20–72 weeks) evaluating oral semaglutide, orforglipron, danuglipron, and lotiglipron were included. All agents except low-dose (LoD) lotiglipron outperformed placebo in percent body weight reduction; high-dose (HiD) semaglutide (MD −11.6%) and orforglipron (MD −11.8%) showed the greatest effects. Orforglipron HiD produced the greatest absolute weight loss (MD −12.2 kg), whereas semaglutide HiD reduced BMI (MD −4.7 kg/m^2) and waist circumference (MD −10.0 cm) the most. Danuglipron HiD, semaglutide HiD, and semaglutide LoD ranked highest for ≥ 5%, ≥ 10%, and ≥ 15% weight loss, respectively. Evidence certainty was low to moderate.

Conclusion: HiD oral semaglutide and orforglipron demonstrated the most consistent and substantial weight reductions though low-to-moderate certainty and lack of head-to-head comparisons constrain comparative inference.

1 | Introduction

Contemporary clinical practice guidelines recommend obesity management medications (OMMs) for adults with obesity and for those with overweight and weight-related comorbidities, especially when structured lifestyle interventions alone fail to achieve or sustain clinically meaningful weight loss [1–4]. Achieving and maintaining 5%–10% weight loss improves glycemia, blood pressure, dyslipidemia, sleep apnea, osteoarthritis, and health-related quality of life, with larger losses ($\geq$ 10–15%) offering greater cardiometabolic benefits. However, durable weight loss with lifestyle modification alone is challenging in routine practice, and most patients require ongoing pharmacologic support to sustain clinically meaningful weight reductions [1–4].

Glucagon-like peptide-1 (GLP-1) receptor agonists (GLP-1 RAs), originally developed for the treatment of type 2 diabetes (T2D), have emerged as a cornerstone pharmacologic option for obesity management. These agents promote weight loss primarily by reducing appetite and energy intake and by slowing gastric emptying, thereby restoring energy balance in an obesogenic environment [5]. Large randomized controlled trials (RCTs) of injectable GLP-1 RAs and dual incretin agonists have demonstrated robust, sustained weight loss of approximately 10%–20% among people with obesity without diabetes, along with improvements in multiple cardiometabolic risk factors [6, 7]. On this basis, regulatory authorities have approved agents such as liraglutide 3.0 mg, semaglutide 2.4 mg, and the dual GLP-1/glucose-dependent insulinotropic polypeptide agonist tirzepatide for chronic weight management as adjuncts to lifestyle interventions in individuals without T2D [1–4].

Despite their efficacy, injectable OMMs are constrained by several practical and psychological barriers that limit their long-term use [8, 9]. Subcutaneous administration requires patients to learn injection techniques, manage injection devices, and dispose of needles, which many perceive as intrusive and incompatible with daily routines [10]. Common adverse effects, such as injection-site pain, bruising, nodules, and dose-dependent gastrointestinal symptoms, can reduce tolerability and make long-term therapy less feasible in routine care [8, 9]. Fear or discomfort with needles is relatively common among individuals receiving preventive care or chronic injection-based treatments, and may, together with other factors, contribute to treatment burden and reluctance to initiate or continue injectable therapies. [11] These may cause patients to skip doses without supervision, extend dosing intervals, or stop treatment suddenly. Real-world data indicate that persistence and adherence to injectable GLP-1–based OMMs are considerably lower than in clinical trials, with a large proportion of individuals discontinuing treatment within the first year, underscoring that these tolerability and convenience issues translate into early drop-off in everyday practice [12–15]. These patterns of non-persistence diminish the cardiometabolic benefits observed in RCTs and underscore the need for equally effective yet less intrusive oral GLP-1 RAs that may better support long-term adherence among people with obesity.

Recently, orally effective peptide and non-peptide GLP-1 RAs have been developed, offering benefits such as easier administration, improved patient adherence, and greater acceptance compared with injectable treatments [16]. Oral semaglutide, a peptide co-formulated with an absorption enhancer to facilitate gastric uptake, is approved for glycemic control in T2D and, more recently, for chronic weight management in adults with obesity [17]. In Phase 2 and 3 obesity trials, higher oral doses (25–50 mg) have produced double-digit percentage weight loss, with a safety profile dominated by transient gastrointestinal events similar to those observed with injectable semaglutide [18–20]. In parallel, several nonpeptide, small-molecule oral GLP-1 RAs—such as orforglipron, danuglipron, and lotiglipron—have been designed to bind the GLP-1 receptor with high potency, enabling once- or twice-daily oral dosing without the need for coformulated absorption enhancers or stringent fasting requirements [16]. These molecules differ from injectable peptides in their pharmacokinetic properties, including oral bioavailability and half-life, but early-phase and phase 2–3 trials have shown clinically meaningful weight loss across a range of doses in adults with overweight or obesity [21–25]. Since long-term safety and efficacy have been established, small-molecule oral GLP-1 RAs could offer practical benefits. These include easier administration, no need for cold-chain storage, and potentially reduced manufacturing costs, which might help expand access, especially in resource-limited settings [16]. Orally administered GLP-1 RAs could collectively allow many patients with obesity, especially those in primary care, to switch from injections, while still achieving guideline-based weight-loss goals when combined with lifestyle interventions [26].

Several prior systematic reviews and meta-analyses have evaluated oral GLP-1 RAs, but they have important limitations for informing treatment decisions in adults with overweight or obesity without diabetes [27–29]. Many have focused solely on oral semaglutide, pooled data from populations with and without T2D, or evaluated small-molecule oral GLP-1 RAs at the class level without distinguishing dose tiers. Most earlier analyses also relied on pairwise comparisons and did not provide a unified comparative ranking across all available oral agents and doses anchored to a common comparator [27–29]. Furthermore, formal assessment of the certainty of evidence using a framework tailored to network meta-analysis, such as Confidence in Network Meta-Analysis (CINeMA), has not been conducted [30]. As a result, clinicians currently lack a comprehensive, comparative synthesis of oral GLP-1 RAs and dose tiers for adults with overweight or obesity without T2D, and the strength of evidence for cross-agent comparisons remains uncertain.

Network meta-analysis (NMA) offers a methodologically rigorous approach to addressing this gap by synthesizing direct and indirect evidence from placebo-controlled RCTs to estimate relative treatment effects across multiple interventions that have not been compared head-to-head. A frequentist random-effects NMA can provide comparative estimates and treatment rankings while formally evaluating heterogeneity, inconsistency, and confidence in the network [31]. In this context, an NMA restricted to adults with overweight or obesity without diabetes, incorporating CINeMA to quantify the certainty of the evidence, can inform treatment selection and future trial design for oral GLP-1 RAs used as adjuncts to lifestyle interventions. This NMA's objective was to compare oral GLP-1 RAs and dose tiers for body-weight outcomes in adults with overweight or obesity

without T2D to inform treatment selection and future trial design.

2 | Methods

2.1 | Search Strategy

Several databases and registries, including PubMed, Scopus, Web of Science, and ClinicalTrials.gov, were systematically searched. The search spanned these sources from their inception to 30 April 2026. Using the Boolean operators "AND" and "OR," the following terms were searched: "obesity," "overweight," "oral glucagon-like peptide-1 receptor agonist," "oral GLP-1 receptor agonist," "oral GLP-1 agonist," "oral semaglutide," "orforglipron," "LY-3502970," "danuglipron," "PF-06882961," "lotiglipron," "PF-07081532," "aleniglipron," "GSBR-1290," "TERN-601,"." The search terms targeted the titles, abstracts, and keywords of the documents, with no language restriction, to find published studies. The full search strategies are provided in a Supporting Information S1: Appendix 1. Additionally, the process included reviewing the references cited in the articles gathered for this research and in relevant journals.

2.2 | Study Selection

The PICOS (Population, Intervention, Comparison, Outcomes, and Study) framework guided the development of eligibility criteria for the clinical trials included in this NMA. The patient population (P) consisted of individuals with obesity or overweight. The intervention (I) included any oral GLP-1 RA, while the control (C) group received a placebo; both groups also received lifestyle recommendations. The outcomes (O) included body weight changes from baseline (percentage and absolute) at the end of the study. Only RCTs with a minimum duration of 12 weeks and participants aged 18 years or older were considered the study type (S) for inclusion. The trials had at least two treatment groups: one receiving any oral GLP-1 RA with lifestyle interventions, and the other a placebo comparator with lifestyle interventions. Excluded from the analysis were non-randomized trials, retrospective studies, pooled clinical trial analyses, conference proceedings, letters to editors, case reports, and articles lacking outcome data of interest. Additionally, studies involving animals or normal-weight humans as well as RCTs shorter than 12 weeks were excluded.

2.3 | Outcomes Analyzed

The primary outcome of interest was the percent change in body weight from baseline at the end of the study. The secondary outcomes included the absolute change in body weight, changes in body mass index (BMI) and waist circumference, and the proportions of study subjects who lost $\geq 5\%$, $\geq 10\%$, or $\geq 15\%$ of body weight from baseline.

2.4 | Data Extraction

Three authors independently extracted data using standard forms. When multiple publications originated from the same study group, their results were combined, and relevant data from each report were included in the analysis. Patient characteristics, including demographic details and comorbidities, from both included and excluded studies were recorded. For the review, the data were extracted from all eligible studies on several key factors: first author, publication year, clinical trial unique identifier, study design and settings, major inclusion criteria, study arms, sample size, percentage of female participants, mean age, baseline body weight, BMI, waist circumference, and study duration. Data on both primary and secondary outcomes were also collected, as previously mentioned. For continuous outcomes, mean differences (MDs) and standard deviations (SDs) between baseline and end-of-study values were extracted. The data were converted to MD ($\pm$ SD) when reported in other formats (e.g., median, confidence intervals [CIs]) using the web-based Meta-Analysis Accelerator [32]. For categorical variables, the number of participants who achieved the specific outcome and the total number of participants were recorded. The supplementary materials of the relevant studies were carefully reviewed. All pertinent information was obtained through written email communication with the corresponding author of the relevant article and was thoughtfully incorporated into the meta-analysis.

2.5 | Risk of Bias Assessment

Three authors independently assessed risk of bias (RoB) using version 2 of the Cochrane risk-of-bias tool for randomized trials (RoB 2) [33]. The domains covered by RoB 2 encompass all types of bias currently recognized as affecting RCT results, including bias arising from randomization, deviations from intended interventions, missing outcome data, outcome measurement, and the selection of reported results. The RoB judgment categorized each domain into one of three levels: low RoB, some concerns, or high RoB. The least favorable assessment across the bias domains was used to determine the overall RoB for the result [33]. Disagreements were settled through consensus. Publication bias was assessed visually using funnel plots, followed by Egger's test for a quantitative assessment [34].

2.6 | Statistical Analysis

Transitivity assumptions were assessed by comparing the distributions of key effect modifiers—such as age, sex, baseline BMI, baseline weight, trial duration, geography, and trial phase or design—across different trials and treatment comparisons. These variables were compiled into a table (Table 1) to evaluate the clinical validity of indirect comparisons. A frequentist random-effects NMA was performed in R Statistical Software (RStudio, Version 2025.09.2 + 418), primarily using the netmeta package, which estimates treatment effects and their uncertainty based on long-run frequency properties without specifying prior distributions, in contrast to Bayesian approaches [31, 35]. Effect estimates for both primary and secondary outcomes were presented as MDs for continuous outcomes and odds ratios [ORs] for binary outcomes, along with 95% CIs, for each comparison against the reference treatment, i.e., placebo.

To explore dose–response relationships and clinical dosing variation, oral GLP-1 RAs were grouped by dose. Network plots were produced to visualize the structure and connectivity of the treatment comparisons, illustrating direct and indirect evidence pathways. Pairwise comparisons for all treatment pairs were generated to provide comprehensive effect estimates from the

TABLE 1 | Characteristics of the included studies and study participants.

Study ID, clinical trial reg. no. [Ref.]	Study design and settings	Major inclusion criteria	Study arm(s)	*N*	Female (%)	Age (years) (mean ± SD)	Body weight (kg) (mean ± SD)	BMI (kg/m^2) (mean ± SD)	WC (cm) (mean ± SD)	Duration of follow up	Primary endpoint
Amin 2025[a], NCT05579977 [21]	Phase 2, double blind, dose ranging, parallel group RCT in Bulgaria, Czech Republic, Hungary, Poland (T2D cohort) and Canada, Japan, United States (had two cohorts: One with T2D and the other with obesity without T2D; we included the second cohort)	18–75 years aged, BMI ≥ 30 kg/m^2, HbA1c ≤ 6.4% and FPG ≤ 126 mg/dL	Lotiglipron 80 mg QD	66	57.6	49.3 ± 13.0	105.7 ± 22.3	37.1 ± 5.7	NR	20 weeks	Change from baseline in HbA1c (T2D cohort) and percentage change from baseline in body weight (obesity cohort)[a]
			Lotiglipron 140 mg QD	64	70.3	48.1 ± 12.4	106.7 ± 25.3	38.4 ± 7.1			
			Lotiglipron 200 mg QD (5-step titration)	65	55.4	47.6 ± 13.5	108.2 ± 21.7	37.9 ± 5.7			
			Lotiglipron 200 mg QD (4-step titration)	66	63.6	50.0 ± 10.7	104.1 ± 15.9	37.0 ± 4.5			
			Lotiglipron 260 mg QD	64	62.5	48.5 ± 11.7	109.3 ± 24.9	38.3 ± 7.3			
			Placebo	64	56.3	50.9 ± 13.3	109.7 ± 22.1	37.9 ± 6.7			
Buckeridge 2025, NCT04707313 [22]	Dose ranging, phase 2b RCT in Canada, United states, Japan	Aged 18–75 years, non-diabetic with BMI ≥ 30 kg/m^2	*Cohort 1 & 2*							*Cohort 1 & 2:* 26 weeks; *Cohort 3:* 32 weeks	Percentage change in body weight from baseline to the end of treatment
			Danuglipron 40 mg BID (1 week)	62	65	47 (median)	109.6 ± 24.0	38.7 ± 7.0	114.4 ± 15.7		
			Danuglipron 80 mg BID (1 week)	63	65	47 (median)	107.6 ± 22.2	38.8 ± 5.9	115.9 ± 13.3		
			Danuglipron 120 mg BID (1 week)	64	66	52 (median)	103.8 ± 16.4	37.5 ± 5.1	112.3 ± 12.5		
			Danuglipron 120 mg BID (2 weeks)	38	58	50 (median)	113.2 ± 22.9	39.4 ± 6.5	120.3 ± 13.8		
			Danuglipron 160 mg BID (1 week)	63	65	48 (median)	106.0 ± 20.1	38.4 ± 5.8	114.7 ± 13.3		

(Continues)

TABLE 1 | (Continued)

Study ID, clinical trial reg. no. [Ref.]	Study design and settings	Major inclusion criteria	Study arm(s)	*N*	Female (%)	Age (years) (mean ± SD)	Body weight (kg) (mean ± SD)	BMI (kg/m^2) (mean ± SD)	WC (cm) (mean ± SD)	Duration of follow up	Primary endpoint
			Danuglipron 160 mg BID (2 weeks)	37	59	45 (median)	113.4 ± 26.8	38.6 ± 8.1	116.7 ± 16.0		
			Danuglipron 200 mg BID (1 week)	63	65	48 (median)	106.9 ± 18.8	38.2 ± 6.4	116.1 ± 14.5		
			Danuglipron 200 mg BID (2 weeks)	36	64	52 (median)	114.6 ± 28.5	40.1 ± 7.0	119.0 ± 17.9		
			Placebo	71	63	49 (median)	109.1 ± 20.8	38.7 ± 5.7	116.1 ± 13.4		
			Cohort 3								
			Danuglipron 80 BID mg (4 weeks)	37	62	49 (median)	112.5 ± 19.5	39.2 ± 4.7	121.9 ± 15.2		
			Danuglipron 140 BID mg (4 weeks)	37	62	51 (median)	115.1 ± 28.3	39.9 ± 9.3	122.2 ± 20.6		
			Danuglipron 200 BID mg (4 weeks)	36	61	48 (median)	117.6 ± 20.2	40.5 ± 6.4	124.3 ± 16.3		
			Placebo	19	63	48 (median)	119.2 ± 29.8	40.9 ± 7.8	122.1 ± 16.9		
Gabe 2024, NCT05236517 [39]	Parallel-group, double-blind, Phase 1 RCT in Germany	Aged 18–65 years with BMI of 30.0–45.0 kg/m^2	Semaglutide 50 mg	30	40	44.0 ± 11.0	105.2 ± 17.9	35.0 ± 3.8	NR	20 weeks	Relative change in energy intake (%) during an ad libitum lunch from baseline at week 20
			Placebo	31	29	43.0 ± 11.0	106.9 ± 14.1	34.8 ± 3.8			
Kadowaki 2025[b], NCT05132088 [18]	Phase 3a double-blind RCT in Japan and South Korea (OASIS 2)	Aged ≥ 18 years (≥ 20 years in Japan), with BMI ≥ 35 kg/m^2 with > 1 weight-related complications or BMI 27 to	Semaglutide 50 mg	134	39.6	49.7 ± 11.1	92.7 ± 18.4	32.9 ± 4.7	105.5 ± 11.7	68 weeks	Percentage change in body weight from baseline and the proportion of participants who achieved 5% or greater body
			Placebo	67	50.7	48.9 ± 11.6	90.3 ± 17.8	32.8 ± 4.7	104.3 ± 12.1		

(Continues)

TABLE 1 | (Continued)

Study ID, clinical trial reg. no. [Ref.]	Study design and settings	Major inclusion criteria	Study arm(s)	*N*	Female (%)	Age (years) (mean ± SD)	Body weight (kg) (mean ± SD)	BMI (kg/m^2) (mean ± SD)	WC (cm) (mean ± SD)	Duration of follow up	Primary endpoint
		< 35 kg/m^2 with > 2 weight-related complications									weight reductions at week 68
Katrevula 2025, NCT05442450 [40]	Phase 4, randomized, open-label, controlled trial was conducted in India	≥ 18 years with a BMI ≥ 30 or ≥ 27 with one or more weight-related comorbidities	Semaglutide 14 mg	58	31.1	43 ± 10	88.9 ± 14.8	32.6 ± 3.1	108.3 ± 8.6	28 weeks	Proportion of patients who achieved a reduction of at least 5% in body weight from baseline at week 28
			Placebo	58	41.4	44 ± 9	93.1 ± 14.8	33.8 ± 4.2	111.0 ± 9.2		
Knop 2023, NCT05035095 [19]	Phase 3, double-blind, superiority RCT in Canada, United states, Japan, Denmark, Finland, France, Germany, Poland and Russia (OASIS 1)	≥ 18 years (≥ 20 years in Japan) aged non-diabetic with BMI ≥ 30 kg/m^2 or BMI 27 to < 30 kg/m^2 with > 1 weight-related coexisting conditions	Semaglutide 50 mg	334	74	49.0 ± 13.0	104.5 ± 22.0	37.3 ± 6.3	112.6 ± 13.6	68 weeks	Percentage change in bodyweight and whether participants reached a bodyweight reduction of at least 5% at week 68
			Placebo	333	71	50.0 ± 12.0	106.2 ± 22.3	37.7 ± 6.8			
Wharton 2023, NCT05051579 [23]	Phase 2, double-blind RCT in Canada, the United States, and Hungary (GZGI)	18–75 years of age, non-diabetic, BMI ≥ 30 kg/m^2 or BMI 27 to < 30 kg/m^2 with > 1 weight-related coexisting conditions	Orforglipron 12 mg	50	62	49.8 ± 10.5	107.5 ± 25.3	37.7 ± 7.7	114.4 ± 16.5	36 weeks	Percentage change from baseline in body weight was assessed at week 26
			Orforglipron 24 mg	53	57	57.0 ± 9.1	112.1 ± 30.2	38.1 ± 7.7	120.1 ± 19.1		
			Orforglipron 36 mg (subcohort 1)	29	62	56.3 ± 11.8	107.8 ± 22.5	38.0 ± 6.4	116.2 ± 16.2		
			Orforglipron 36 mg (subcohort 2)	29	62	55.4 ± 10.9	108.8 ± 28.5	38.0 ± 6.3	118.4 ± 14.7		
			Orforglipron 45 mg (subcohort 1)	31	61	56.5 ± 10.7	105.2 ± 20.4	36.8 ± 5.5	116.1 ± 12.8		

(Continues)

TABLE 1 | (Continued)

Study ID, clinical trial reg. no. [Ref.]	Study design and settings	Major inclusion criteria	Study arm(s)	*N*	Female (%)	Age (years) (mean ± SD)	Body weight (kg) (mean ± SD)	BMI (kg/m^2) (mean ± SD)	WC (cm) (mean ± SD)	Duration of follow up	Primary endpoint
			Orforglipron 45 mg (subcohort 2)	30	53	50.9 ± 12.6	110.9 ± 28.1	38.7 ± 7.6	117.7 ± 14.8		
			Placebo	50	58	54.0 ± 8.8	107.6 ± 25.2	37.8 ± 6.5	115.5 ± 15.4		
Wharton 2025 (O), NCT05869903 [24]	Phase 3, double-blind RCT in the United States, Brazil, China, India, Japan, South Korea, Taiwan, Puerto Rico, Slovakia, and Spain (ATTAIN-1)	≥ 18 years of aged non-diabetic with BMI ≥ 30 kg/m^2 or BMI between 27 and 30 kg/m^2 with ≥ 1 obesity-related complication, and history of at least one unsuccessful dietary effort to lose body weight	Orforglipron 6 mg	723	64.9	44.9 ± 12.1	103.2 ± 21.7	37.0 ± 6.5	112.1 ± 14.1	72 weeks	Percent change in body weight from baseline to week 72
			Orforglipron 12 mg	725	64.4	45.4 ± 12.6	102.2 ± 21.6	36.7 ± 6.5	112.0 ± 14.2		
			Orforglipron 36 mg	730	63.7	44.9 ± 11.9	103.1 ± 23.2	36.9 ± 6.7	112.4 ± 15.3		
			Placebo	949	64.1	45.1 ± 11.9	103.9 ± 22.0	37.1 ± 6.3	112.8 ± 14.5		
Wharton 2025 (S), NCT05564117 [20]	Phase 3, double-blind RCT in Canada, Germany, Poland, and the United States (OASIS 4)	≥ 18 years aged non-diabetic with BMI ≥ 30 kg/m^2 or BMI > 27 kg/m^2 with > 1 weight-related coexisting conditions and those who reported at least one unsuccessful dietary effort to lose weight	Semaglutide 25 mg	205	75.6	48.0 ± 13.0	106.4 ± 23.5	37.5 ± 6.7	114.0 ± 15.8	64 weeks	Percent change in body weight and a reduction of 5% or more in body weight at week 64
			Placebo	102	85.3	47.0 ± 13.0	104.8 ± 19.7	37.8 ± 6.1	113.6 ± 14.7		

Abbreviations: BD, twice daily; BMI, body mass index; CV, cardiovascular; FPG, fasting plasma glucose; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycated hemoglobin; NR, not reported; OD, once daily; OW, once weekly; RCT, randomized control trial; T2D, type 2 diabetes; WC, waist circumference.

[a]The study was terminated early for safety reasons after routine data and monitoring review. The planned analyses for the endpoints were modified prior to unblinding the study.

[b]The study involved subjects with overweight or obesity, with or without type 2 diabetes. The baseline characteristics were for all the study subjects. The outcome data for those without type 2 diabetes (n = 147) were analyzed.

NMA. Inconsistency analyses were conducted to evaluate the agreement between direct and indirect evidence across the network, utilizing the "netsplit" function with the back-calculation method. Treatment effects were ranked from best to worst along the leading diagonal, and the results were presented as league tables. P-scores were calculated to rank treatments by relative effectiveness on a 0–1 scale, representing the mean extent of certainty that a given treatment is better than competing treatments, based on point estimates and standard errors from the NMA. Higher P-scores indicate greater relative effectiveness, but they are not p values and do not quantify statistical significance. Statistical significance was set at the 0.05 level. Statistical heterogeneity was evaluated using Cochrane's Q test and the I^2 statistic [36]. The restricted maximum-likelihood estimator was applied to estimate tau^2, and I^2 was calculated based on Q.

2.7 | Assessment of the Certainty of Evidence

The certainty of evidence was systematically assessed using the Confidence In Network Meta-Analysis (CINeMA) framework [30]. This framework evaluates six domains: within-study bias (risk of bias), across-study bias (publication bias), indirectness, imprecision, heterogeneity, and incoherence. Judgments for each CINeMA domain were used to provide an overall certainty rating for the comparison (high, moderate, low, or very low) [30].

2.8 | Ethical Statement

This NMA was registered prospectively with PROSPERO (CRD420251157753), and the protocol summary is available online. It was carried out in accordance with the Cochrane Handbook for Systematic Reviews of Interventions [37], and the reporting conformed to the PRISMA-NMA guidelines [38]. No separate ethical approval was required for this NMA, as approval had already been obtained for the individual RCTs included.

3 | Results

3.1 | Search Results

The study selection process is shown in Figure 1. An initial search yielded 689 articles; after screening titles, abstracts, and full texts, this was reduced to 11. Ultimately, nine RCTs with nine published reports involving 5766 participants, with follow-up durations ranging from 20 to 72 weeks, that met all predefined criteria were included in this NMA [18–24, 39, 40]. Two short-duration Phase 1 trials were excluded (Supporting Information S1: Table S1) [25, 41].

3.2 | Characteristics of Included Studies

The summaries of the included and excluded studies are shown in Table 1 and Supporting Information S1: Table S1, respectively. Of the nine included RCTs, Gabe 2024 was a Phase 1 trial [39]; Amin 2025, Buckeridge 2025, and Wharton 2023 were Phase 2 trials [21–23]; Kadowaki 2025, Knop 2023, Wharton 2025 (O), and Wharton 2025 (S) were Phase 3 trials [18–20, 24]; and Katrevula 2025 was a Phase 4 trial [40]. Amin et al. (2025) studied two cohorts: the T2D cohort and the obesity cohorts; we included only the obesity cohorts [21]. Kadowaki 2025 included adults with obesity (N = 201) with or without diabetes; we analyzed the subset without diabetes (n = 147) in this NMA [18]. Adults with obesity comprised the study subjects in the other studies. In the intervention group, one study included lotiglipron [21], another included danuglipron [22], five used oral semaglutide [18–20, 39, 40], and two used orforglipron [23, 24]; all used placebo controls. To explore dose–response relationships, doses were categorized into low-dose (LoD), medium-dose (MeD), and high-dose (HiD) tiers, informed by dose-finding data and trial protocols. For danuglipron, doses of 40–80 mg were labeled LoD, 120–140 mg as MeD, and 160–200 mg as HiD, reflecting lower versus near-maximal exposures used in the phase 2b obesity study [22]. For orforglipron, 6–12 mg was treated as LoD, 24–36 mg as MeD, and 45 mg as HiD, aligning with the stepped escalation used in ATTAIN-1 and earlier studies [23, 24]. For lotiglipron, 80 mg, 140 mg, and 200–260 mg were designated LoD, MeD, and HiD, respectively, based on dose-ranging data [21]. For oral semaglutide, doses were categorized as 14 mg (LoD), 25 mg (MeD) and 50 mg (HiD), consistent with phase 2-3 dose-finding programs [18–20, 39, 40]. Neighboring doses within the same tier and across titration schedules (e.g., 200 mg lotiglipron with 4-step vs. 5-step titration) were combined because the magnitude of weight loss appeared more closely related to the target maintenance dose than to titration details [21, 22]. Nevertheless, this grouping may introduce residual heterogeneity and reduce the granularity of dose–response inferences. The separate results provided in Buckeridge 2025 for cohorts 1 and 2 and for cohort 3 were analyzed separately. Placebo groups were distinct within each cohort with no participant overlap, allowing these cohorts to be treated as independent nodes in the network [22].

The follow-up periods of the RCTs ranged from 20 to 72 weeks. Across trials, mean age, baseline body weight, and BMI were broadly similar, but there were important differences in geography, phase, sex distribution, study duration, and primary endpoints. Gabe 2024 was a Phase 1 study primarily designed to evaluate appetite, gastric emptying, and energy intake; however, it included 20 weeks of follow-up and systematically reported body-weight change, meeting the $\geq$ 12-week duration criterion [39]. Kadowaki 2025 enrolled an East Asian population with a lower baseline BMI than Western cohorts; only the non-diabetic subset was included in the present NMA [18]. Katrevula 2025 was an open-label Phase 4 trial with liver fibrosis as the primary endpoint and weight loss as a prespecified secondary outcome [40]. Amin 2025, the sole lotiglipron trial, was terminated early due to elevations in liver enzymes [21]. Similarly, danuglipron development, reported in only one study (Buckeridge 2025), was later discontinued despite robust weight-loss efficacy [22]. These design differences likely contributed to heterogeneity and were accounted for in our qualitative assessment of transitivity (Table 1). The baseline characteristics of the included RCTs were consistent across all trial arms. Supporting Information S1: Table S2 provides the results of individual studies, including summary data for each intervention group.

3.3 | Risk of Bias in the Included Studies

Supporting Information S1: Figure S1 illustrates the specific and overall RoB in the nine included RCTs. The overall RoB was low in four (44.4%) trials. Three (33.3%) studies raised "some concerns" about bias, either from deviations from the intended

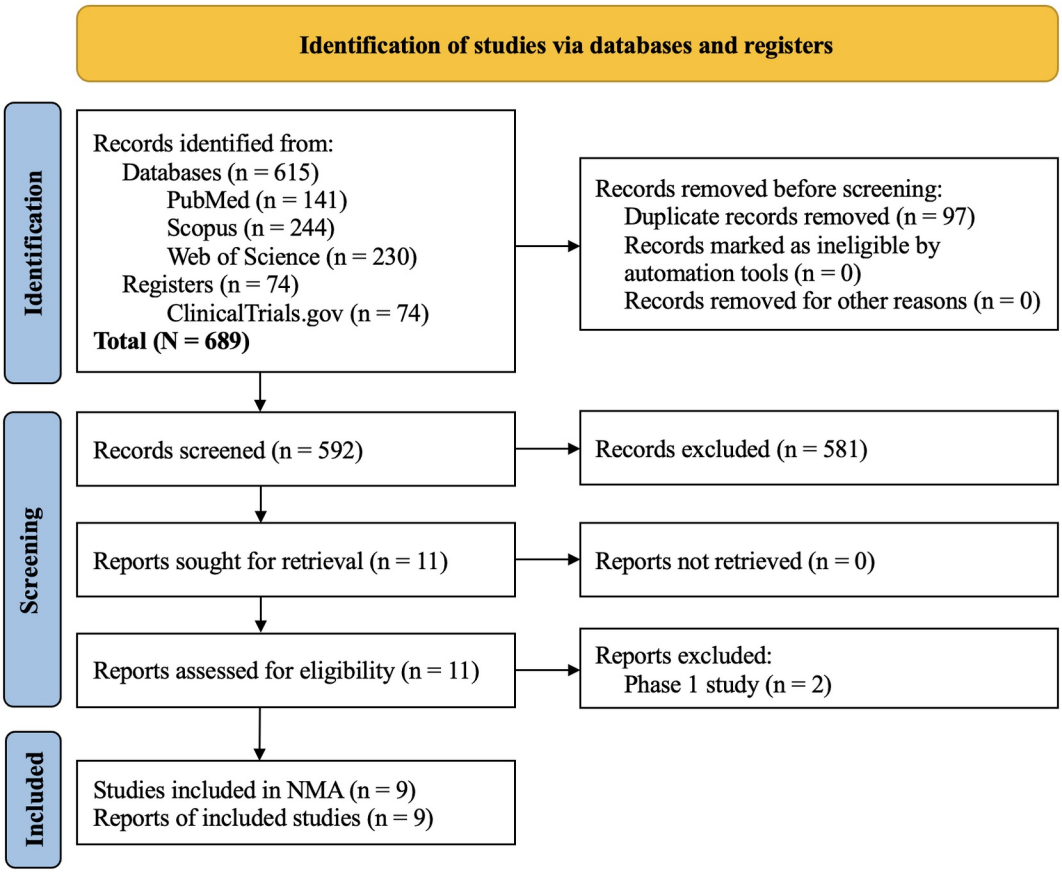

FIGURE 1 | Flowchart of study retrieval and inclusion in the meta-analysis.

intervention (Katrevula 2025) or from issues in the randomization process [Wharton 2023 and Wharton 2025 (O)] [23, 24, 40]. The remaining two (22.3%) had a high risk of bias due to missing outcome data [21, 22]. The comparison-adjusted funnel plot for the percent changes in body weight (Supporting Information S1: Figure S2) appears largely symmetrical with an Egger's test p-value of 0.0572, suggesting only borderline evidence of small-study effects or publication bias. However, publication bias was strongly suspected given the small number of early-phase, sponsor-funded RCTs [34].

3.4 | Percent Change in Body Weight

Nine studies, involving 13 treatments and 5657 observations, were included in the NMA evaluating the impact of oral GLP-1 RAs on the percent change in body weight compared with placebo. Figure 2A presents the network diagram, and Figure 2B presents the NMA forest plot comparing oral GLP-1 RAs with placebo; all active treatments, except lotiglipron LoD (MD = −2.44%, $p = 0.2151$), significantly outperformed placebo. High heterogeneity was evident ($\tau^2 = 3.35$, $I^2 = 73\%$; total $Q = 25.93$, $p = 0.0005$), driven by within-design variation ($Q = 24.39$, $p = 0.0002$), while between-design inconsistency was non-significant ($Q = 1.54$, $p = 0.4624$). Semaglutide HiD (MD −11.6%, P-score = 0.878) and orforglipron HiD (MD −11.8%, P-score = 0.878) were the most effective, followed by semaglutide MeD (MD −11.4%, P-score = 0.845) (Figure 2B,C). Supporting Information S1: Table S3 provides the league table [direct estimates (upper-right triangle) and network estimates (lower-left triangle)]. The netsplit estimates showed no inconsistency between the indirect and direct effects (Supporting Information S1: Figure S3).

3.5 | Absolute Change in Body Weight

Six studies, involving 7 treatments and 4495 observations, were included in the NMA evaluating the impact of oral GLP-1 RAs on the absolute change in body weight compared with placebo. Supporting Information S1: Figures S4A,B present the network diagram and the NMA forest plot comparing oral GLP-1 RAs with placebo, respectively; all active treatments significantly outperformed placebo. High heterogeneity was evident ($\tau^2 = 3.80$, $I^2 = 81.4\%$; total $Q = 16.16$, $p = 0.0011$) driven by within-design variation ($Q = 13.05$, $p = 0.0003$), while between-design inconsistency was non-significant ($Q = 3.11$, $p = 0.2115$). Orforglipron HiD (MD −12.2 kg, P-score = 0.834) was most effective, followed by semaglutide MeD (MD −12.0 kg, P-score = 0.772) and semaglutide HiD (MD −10.9 kg, P-score = 0.708) (Supporting Information S1: Figures S4B,C). Supporting Information S1: Table S4 provides the league table [direct estimates (upper-right triangle) and network estimates (lower-left triangle)]. The netsplit estimates showed no inconsistency between the indirect and direct effects (Supporting Information S1: Figure S4D).

3.6 | Change in Body Mass Index

Five studies, involving 7 treatments and 4434 observations, were included in the NMA evaluating the impact of oral GLP-1 RAs

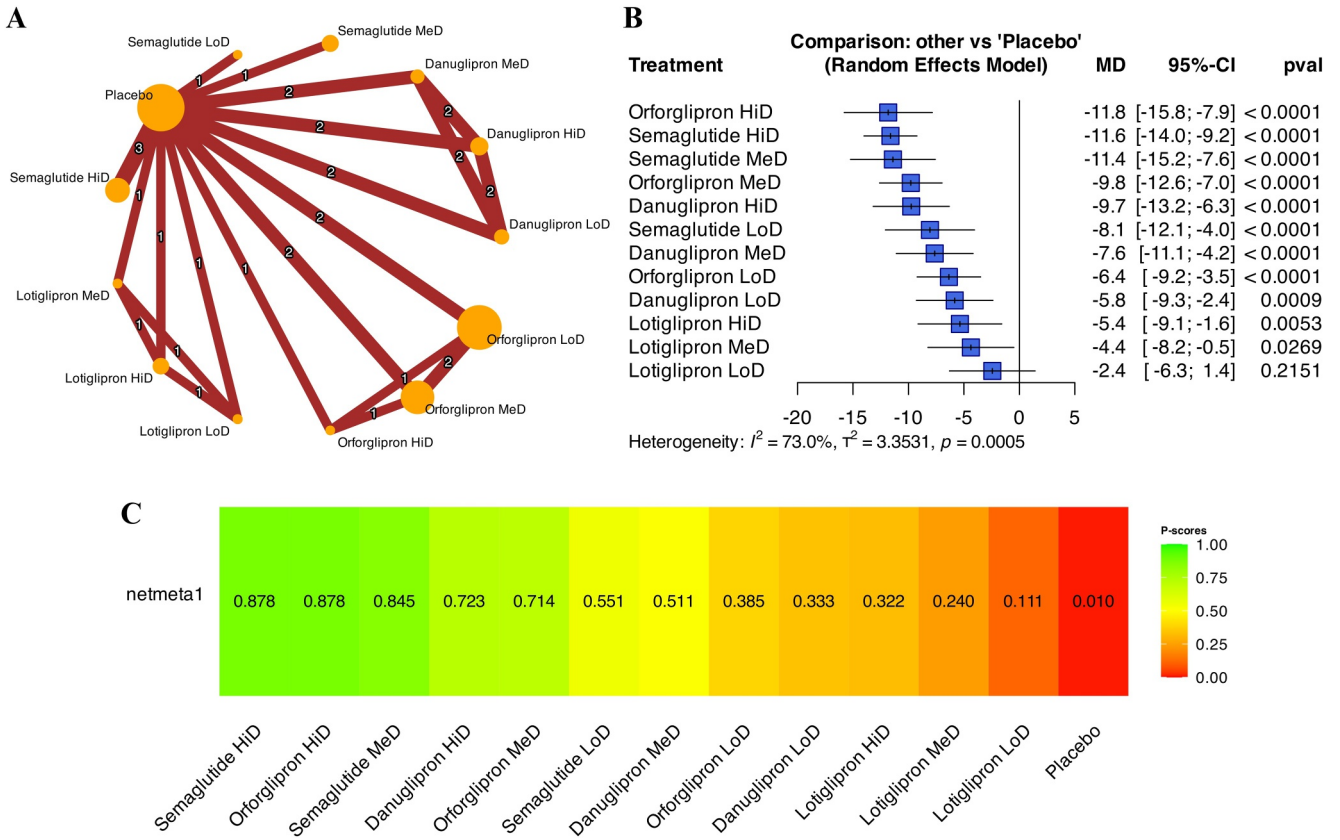

FIGURE 2 | (A) Network diagram of treatment comparisons for percent change in body weight. This network meta-analysis (NMA) graph illustrates comparisons among oral GLP-1 RAs and placebo for the percent change in body weight from baseline. Each node represents a treatment. Lines between nodes indicate direct comparisons, with line thickness reflecting the number of supporting studies. Treatments without direct connections are compared through indirect evidence within the NMA framework. (B) Forest plot for the percent change in body weight. This figure presents the relative effects of treatments on the percent change in body weight from baseline. The forest plot displays mean differences (MDs) with 95% confidence intervals (CIs) for each treatment relative to the reference treatment (placebo). A negative MD indicates a greater percent reduction in body weight. (C) P-score rankings for the percent change in body weight. The P-score ranks treatments by their likelihood of being the most effective at reducing percent body weight, with higher P-scores indicating greater effectiveness.

on the absolute change in BMI compared with placebo. Supporting Information S1: Figures 5A,B present the network diagram and the NMA forest plot comparing oral GLP-1 RAs with placebo, respectively; all active treatments significantly outperformed placebo. Heterogeneity and inconsistency were low (tau^2 = 0.0424, I^2 = 23.9%) and non-significant by Q tests, supporting a coherent random-effect network. Semaglutide HiD (MD −4.7 kg/m^2, *P*-score = 0.911) was most effective, followed by semaglutide MeD (MD −4.3 kg/m^2, *P*-score = 0.776) and orforglipron HiD (MD −4.2 kg/m^2, *P*-score = 0.775) (Supporting Information S1: Figures S5B,C). Supporting Information S1: Table S5 provides the league table [direct estimates (upper-right triangle) and network estimates (lower-left triangle)]. The netsplit estimates showed no inconsistency between the indirect and direct effects (Supporting Information S1: Figure S5D).

3.7 | Change in Waist Circumference

Seven studies, involving 10 treatments and 5060 observations, were included in the NMA evaluating the impact of oral GLP-1 RAs on the absolute change in waist circumference compared with placebo. Supporting Information S1: Figures S6A,SB present the network diagram and the NMA forest plot comparing oral GLP-1 RAs with placebo, respectively. All active treatments significantly outperformed the placebo in decreasing waist circumference. No heterogeneity and inconsistency were found (tau^2 < 0.0001, I^2 = 0%) and were non-significant by Q tests (Total 4.42, p = 0.4904), supporting a coherent random-effects network. Semaglutide HiD (MD −10.0 cm, P-score = 0.924) was most effective, followed by orforglipron HiD (MD -9.4 cm, P-score = 0.858) and semaglutide MeD (MD −9.4 cm, P-score = 0.856) (Supporting Information S1: Figure S6B,C). Supporting Information S1: Table S6 provides the league table [direct estimates (upper-right triangle) and network estimates (lower-left triangle)]. The netsplit estimates showed no inconsistency between the indirect and direct effects (Supporting Information S1: Figure S6D).

3.8 | Weight Loss Thresholds (≥ 5%, ≥ 10%, ≥ 15%)

Seven studies (10 treatments, 4735 observations) evaluated ≥ 5% weight loss. All active treatments significantly outperformed the placebo (Supporting Information S1: Figure S7A,B). Moderate heterogeneity was evident (τ^2 = 0.4097, I^2 = 69.4%) driven by between-design inconsistency (Q = 11.48, p = 0.0032), likely reflecting differences in inclusion criteria, duration, or dose

categorization. Danuglipron HiD (OR 32.6, *P*-score 0.848), semaglutide LoD (OR 27.9, *P*-score 0.766), and orforglipron HiD (OR 18.3, *P*-score 0.646) ranked highest (Supporting Information S1: Figure S7B,C and Table S7). Netsplit analysis showed no inconsistency between direct and indirect estimates (Supporting Information S1: Figure S7D).

Five studies (7 treatments, 4409 observations) evaluated ≥ 10% weight loss. All active treatments significantly outperformed the placebo (Supporting Information S1: Figure S8A,B). Low heterogeneity ($\tau^2 = 0.0272$, $I^2 = 34.9\%$) and no significant inconsistency ($Q = 3.05$, *P*-score = 0.2175) supported network coherence. Semaglutide HiD (OR 16.8, *P*-score 0.927), orforglipron HiD (OR 10.6, *P*-score 0.666), and semaglutide MeD (OR 10.1, *P*-score 0.634) were most effective (Supporting Information S1: Figure S8C,D and Table S8). Direct and indirect estimates were consistent (Supporting Information S1: Figure S8D).

For ≥ 15% weight loss, the same five studies showed that all active treatments significantly outperformed the placebo (Supporting Information S1: Figure S9A,B). No heterogeneity or inconsistency was detected ($\tau^2 < 0.0001$, $I^2 = 0\%$; $Q = 1.69$, $p = 0.4290$). Semaglutide LoD ranked highest (OR 38.1, *P*-score 0.840), followed by semaglutide HiD (OR 18.9, *P*-score 0.812) and semaglutide MeD (OR 17.0, *P*-score 0.758) (Supporting Information S1: Figure S9C,D and Table S9). However, the extremely wide confidence interval for semaglutide LoD (95% CI 2.2–656.5) indicates sparse-data instability; this ranking should not be interpreted as evidence of superior efficacy over higher doses. Netsplit analysis confirmed consistency (Supporting Information S1: Figure S9D).

3.9 | Safety and Tolerability

Across trials, treatment-emergent adverse events were common but generally mild to moderate and consistent with the known GLP-1 RA class profile. Gastrointestinal symptoms (nausea, vomiting, diarrhea, constipation, dyspepsia, and gastroesophageal reflux) were the most frequently reported events and the main reason for treatment discontinuation in active arms. In obesity cohorts receiving danuglipron and lotiglipron, gastrointestinal events occurred in roughly half to three-quarters of participants and drove most treatment-related discontinuations, particularly at higher target doses and with faster titration schedules [21, 22]. In contrast, oral semaglutide (25–50 mg) showed a safety profile characterized by transient, mainly mild-to-moderate gastrointestinal events that peaked during dose escalation, with infrequent serious adverse events occurring at rates similar to placebo [18–20, 39, 40]. Lotiglipron was also associated with dose-related elevations in liver transaminases, with a small proportion of participants having ALT or AST ≥ 3× the upper limit of normal [21].

Together with data from Phase 1 studies, this led to early termination of the Phase 2 program and discontinuation of its clinical development. Danuglipron's development was subsequently halted after a drug-induced liver injury signal in later studies, despite no clear dose-related liver enzyme signal in the Phase 2b obesity trial included in this NMA [22]. No consistent hepatotoxicity signal was reported for oral semaglutide or orforglipron in the included trials, and serious treatment-related adverse events were uncommon overall [18–20, 23, 24, 39, 40]. However, heterogeneous safety reporting and the small number of studies per agent precluded a formal comparative NMA of safety endpoints.

3.10 | Certainty of Evidence: Confidence in Network Meta-Analysis (CINeMA) Assessment

The CINeMA assessment results for the primary outcome are summarized in Figure S10. Overall, confidence in most estimated relative effects was rated as low or moderate. Direct comparisons involving active doses (e.g., danuglipron HiD vs. placebo, orforglipron HiD vs. placebo, and several semaglutide-related comparisons) generally received moderate confidence, mainly downgraded due to some concerns or major concerns about within-study bias and/or reporting bias, but with fewer issues in other domains such as indirectness, imprecision, heterogeneity, or incoherence. In contrast, most comparisons, especially indirect ones between different agents (e.g., danuglipron HiD vs. lotiglipron HiD, orforglipron LoD vs. semaglutide MeD) or dose-level comparisons within agents, were rated with low confidence. These downgrades often resulted from a combination of major concerns about within-study bias, some concerns about reporting bias, and additional issues such as imprecision and heterogeneity. These findings reflect the limited number of studies per comparison, often 1 to 3, as well as common concerns about bias and selective reporting in the underlying trials. Additionally, variable contributions of imprecision or heterogeneity affect several network estimates. The CINeMA evaluations caution against interpreting relative efficacy results too literally, especially for indirect comparisons across agents.

4 | Discussion

This NMA of 5766 participants from 9 RCTs (20–72 weeks) evaluated four oral GLP-1 RAs for weight management in obesity without diabetes. All oral GLP-1 RAs (except lotiglipron LoD) significantly reduced body weight compared with placebo, with mean reductions of 5%–12%. HiD semaglutide and orforglipron demonstrated the most substantial and consistent weight reductions (11%–12%), along with meaningful improvements in BMI and waist circumference. CINeMA assessments rated the evidence as low to moderate confidence, primarily due to bias and imprecision in indirect comparisons. Given the predominantly low-confidence ratings for cross-agent comparisons, treatment rankings should be interpreted as hypothesis-generating rather than definitive evidence of comparative effectiveness.

While semaglutide HiD and orforglipron HiD showed identical P-scores (0.878) for percent weight change, such near-ties indicate statistical indistinguishability within the current evidence base and not true clinical superiority. Discordance between absolute and relative weight-loss metrics likely reflects baseline weight differences across trials rather than pharmacological differences. Some binary outcomes exhibited biologically implausible dose-response reversals (e.g., semaglutide LoD outranking HiD for ≥ 15% weight loss, OR 38.1, 95% CI 2.2–656.5), reflecting sparse-data artifacts rather than true efficacy patterns. Similarly, danuglipron HiD ranked highest for ≥ 5% weight loss, despite semaglutide HiD and orforglipron HiD showing greater effects on

continuous outcomes. These apparent reversals should not be interpreted literally but rather as artifacts of limited events and small sample sizes in certain comparisons.

These results position oral GLP-1 RAs as promising adjuncts to lifestyle interventions for obesity management, addressing injection-related adherence barriers associated with approved injectable GLP-1 RAs [14, 15]. In a recent article, Kushner et al. emphasize that incretin-based obesity pharmacotherapies should be integrated into structured lifestyle interventions rather than used in isolation. The authors highlight practical strategies to align dietary patterns, physical activity, and behavioral counseling with GLP–1–based treatment to enhance weight loss, mitigate gastrointestinal adverse effects, and support long-term adherence. The trial evidence synthesized in this NMA, in which all participants received at least lifestyle advice alongside pharmacotherapy, is consistent with this integrated care model [42]. Achieving 10%–12% weight loss aligns with guideline thresholds for cardiometabolic risk reduction and is associated with substantial improvements in blood pressure, lipids, sleep apnea, metabolic dysfunction-associated steatohepatitis, osteoarthritis symptoms, and health-related quality of life [1–4]. Waist circumference reductions of 9–10 cm suggest decreased visceral adiposity, which has previously been linked to lower cardiovascular risk [43]. However, the cardiovascular benefits of oral GLP-1 RAs for obesity without diabetes remain speculative, based on extrapolations from data on injectable semaglutide in high-risk populations (e.g., the SELECT trial) [44].

Oral semaglutide—already FDA-approved for diabetes and, very recently, for obesity—could pave the way for transitioning from injectable to oral GLP-1 RAs in obesity treatment [17], increasing accessibility in primary care. With the recent FDA approval of orforglipron, newer non-peptide small-molecule GLP-1 RAs may also be suitable options for patients with absorption challenges or needle phobia, pending broader regulatory approval and real-world experience [45]. However, real-world effectiveness, long-term adherence, and cost-effectiveness require further study. In diverse settings such as South Asia, these agents may help address rising obesity rates, though broader regional trials are needed, given that only one included study (Katrevula 2025) enrolled participants from South Asia [40]. Policymakers may consider integrating higher-dose regimens into obesity pharmacotherapy algorithms for individuals who have not achieved adequate weight loss with lifestyle interventions alone, while emphasizing shared decision-making and realistic weight-loss expectations.

Notably, lotiglipron and danuglipron are no longer in clinical development due to hepatotoxicity signals identified during clinical trials. Although these agents showed favorable weight loss in the included studies, elevations in hepatic enzymes led to early program termination [21, 22]. Rankings involving these discontinued molecules have limited clinical relevance and are presented for completeness of evidence rather than to inform practice. Oral semaglutide and orforglipron showed no consistent signals of hepatotoxicity in the included trials, though comprehensive safety surveillance remains essential.

This NMA provides the first comparative synthesis of multiple oral GLP-1 RAs across different dose tiers in obesity without diabetes, demonstrating statistical significance across nearly all anthropometric outcomes. However, several limitations warrant acknowledgment. The transitivity assumption may have been challenged by heterogeneity across trial phases (1–4), populations (East Asian vs. Western cohorts), trial designs (including one open-label study), sample sizes, sex distributions (40%–85% female), study durations (20–72 weeks), and primary endpoints. Meta-regression or subgroup analyses were not performed because there are only nine trials, each with limited data per treatment, which would lead to unstable statistical estimates. Therefore, residual confounding by baseline BMI, geography, or trial duration cannot be ruled out, and comparative rankings should be interpreted with caution. Duration heterogeneity may partly explain the absolute weight-loss differences between short-term (Gabe 2024, 20 weeks) [39] and long-term trials (ATTAIN-1, 72 weeks) [24]. Dose-tier pooling, while clinically pragmatic, may introduce heterogeneity and reduce the granularity of dose-response inferences.

Sparse data led to improbable ranking patterns for certain binary outcomes, suggesting statistical instability instead of genuine relationships. Rankings for lotiglipron and danuglipron are particularly uncertain given the high RoB from missing outcome data, and sensitivity analyses excluding these trials were not conducted. Moderate-to-high heterogeneity across several outcomes is concerning, whereas the apparent absence of heterogeneity in others may reflect limited statistical power due to the small number of studies and events. The absence of head-to-head trials necessitated reliance on placebo-anchored indirect comparisons, introducing indirectness. Borderline publication bias reflects sponsor influence in a small, early-phase RCT pool. Limited subgroup data restrict generalizability primarily to Caucasian adults with moderate-to-severe obesity. Finally, safety outcomes were not pooled quantitatively due to heterogeneous reporting across trials; the findings of this NMA focus on efficacy and do not capture emerging liver safety signals for small-molecule agents. These safety considerations should inform clinical decision-making alongside efficacy data.

Future research should prioritize long-term studies ($>$ 72 weeks) to assess durability after discontinuation, cardiovascular outcomes, real-world effectiveness, comparative safety profiles, cost-effectiveness, and generalizability across diverse populations. Head-to-head trials comparing oral GLP-1 RAs would strengthen the evidence for comparative effectiveness. Until such data emerge, treatment selection should be guided by individual patient factors, safety profiles, accessibility, and shared decision-making, recognizing that current comparative rankings remain exploratory given low-to-moderate-certainty evidence.

5 | Conclusions

This NMA indicates that high-dose oral GLP-1 RAs, notably semaglutide and orforglipron, are associated with greater weight loss than placebo in adults with obesity but not diabetes. Nonetheless, many comparisons rely on limited early-phase trials, and CINeMA ratings were mostly low to moderate; therefore, rankings among agents should be viewed with caution. These drugs appear promising for obesity management,

but their future use will depend on long-term safety data, direct-comparison trials, and real-world evidence.

Author Contributions

A.B.M. Kamrul-Hasan and Deep Dutta conceptualized the NMA. Lakshmi Nagendra, Hamid Ashraf, and Subhankar Chatterjee conducted the literature search. Tahniyah Haq, Mansuor A. Alanazi, and Joseph M. Pappachan provided detailed reviews of the articles. The data were entered by Deep Dutta, Hamid Ashraf, and Subhankar Chatterjee. A.B.M. Kamrul-Hasan, Lakshmi Nagendra, and Ibrahim Khalil conducted the statistical analysis. Deep Dutta and Joseph M Pappachan adjudicated any disagreements. A.B.M. Kamrul-Hasan, Hamid Ashraf, Subhankar Chatterjee, and Joseph M Pappachan wrote the draft, and Lakshmi Nagendra, Ibrahim Khalil, Deep Dutta, Tahniyah Haq, and Mansuor A. Alanazi reviewed and revised the manuscript. Each author made contributions to the article and approved it for submission. The manuscript has been read and approved by all authors for submission to this journal for consideration for publication.

Acknowledgments

AI tools were used solely for linguistic refinement and formatting assistance. No AI tool was involved in the generation of research data, interpretation of results, or formulation of conclusions. All AI-generated outputs were critically reviewed and revised by the authors.

Funding

The authors have nothing to report.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.

Supporting Information S1: osp470181-sup-0001-suppl-data.docx. **FIGURE S10:** Confidence in network meta-analysis (CINeMA) assessment of percent change in body weight for all pairwise comparisons

among oral GLP-1 receptor agonists and placebo. The figure displays, for each direct and indirect comparison, the number of contributing studies, domain-level judgments for within-study bias, reporting bias, indirectness, imprecision, heterogeneity, and incoherence (green = no concerns, yellow = some concerns, red = major concerns), and the resulting overall confidence rating (high, moderate, low, or very low) with reasons for downgrading (e.g., within-study bias, reporting bias, imprecision, heterogeneity).