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REVIEW

Efficacy and Safety of Glucagon-Like Peptide-1 Receptor Agonists for Weight Loss Among Adults Without Diabetes

A Systematic Review of Randomized Controlled Trials

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Background: Recent randomized controlled trials (RCTs) have investigated glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and dual or triple co-agonists for weight loss among adults with overweight or obesity and without diabetes.

Purpose: To assess the efficacy and safety of GLP-1 RAs and co-agonists for the treatment of obesity among adults without diabetes.

Data Sources: MEDLINE, Embase, and Cochrane CENTRAL from inception to 4 October 2024.

Study Selection: Placebo-controlled RCTs in otherwise healthy participants with overweight or obesity.

Data Extraction: The primary outcome was change in relative or absolute body weight from baseline to maximum on-treatment follow-up. Safety outcomes included death, serious adverse events (SAEs), any adverse events (AEs), and gastrointestinal AEs.

Data Synthesis: A total of 26 RCTs comprising 15 491 participants (72% female; mean body mass index, 30 to 41 kg/m^2; mean age, 34 to 57 years) and 12 agents (3 commercially available agents [liraglutide, semaglutide, and tirzepatide] and 9 premarket agents for long-term weight management) were included. Treatment ranged from 16 to 104 weeks (median, 43 weeks). Compared with placebo, tirzepatide (15 mg once weekly) resulted in weight loss of up to 17.8% (95% CI, 16.3% to 19.3%) after 72 weeks of therapy; semaglutide (2.4 mg once weekly), up to 13.9% (CI, 11.0% to 16.7%) after 68 weeks; and liraglutide (3.0 mg once daily), up to 5.8% (CI, 3.6% to 8.0%) after 26 weeks. Retatrutide (12 mg once weekly) produced greater weight loss of up to 22.1% (CI, 19.3% to 24.9%) after 48 weeks; other novel single and combination GLP-1 agents were also efficacious to varying degrees. Although AEs were frequent (GLP-1 RA vs. placebo: 80% to 97% vs. 63% to 100%), the majority were gastrointestinal-related (47% to 84% vs. 13% to 63%, respectively), most commonly nausea, vomiting, diarrhea, and constipation. AEs requiring treatment discontinuation (0% to 26% vs. 0% to 9%, respectively) and SAEs (0% to 10% vs. 0% to 12%, respectively) were rare.

Limitations: No head-to-head RCTs were available. Heterogeneity prevented meta-analysis.

Conclusion: GLP-1 RAs and co-agonists are efficacious for weight loss, with reported safety concerns predominantly gastrointestinal in nature, when used among adults with overweight or obesity and without diabetes.

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Although initially developed to treat type 2 diabetes, glucagon-like peptide-1 receptor agonists (GLP-1 RAs) result in substantial weight loss among people with overweight or obesity independent of diabetes diagnosis (1, 2). Current U.S. Food and Drug Administration–approved GLP-1 RAs for weight management include injectable liraglutide, semaglutide, and tirzepatide (3). Research is ongoing to develop novel GLP-1 RAs with enhanced properties for weight management (4). These novel agents include combination dual or triple agonists that may offer increased efficacy via targeting of multiple incretin pathways involved in appetite regulation and metabolism, such as glucose-dependent insulinotropic polypeptide (GIP) and glucagon (GCG) (5). Oral agents are also being investigated in the context of obesity (5). Although GLP-1 RAs and co-agonists have been investigated in multiple randomized controlled trials (RCTs), their overall efficacy and safety profiles remain unknown. Therefore, we conducted a systematic review to assess the efficacy and safety of GLP-1 RAs and co-agonists for the treatment of overweight or obesity in adults without diabetes.

Methods

Our systematic review was conducted according to a prespecified protocol, which was publicly registered with PROSPERO (CRD42024505558). This study

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is reported as per the 2020 PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) statement (6) and the SWiM (Synthesis Without Meta-analysis) reporting guidelines (7).

Data Sources and Search Strategy

We systematically searched MEDLINE (via PubMed), Embase (via Ovid), and Cochrane CENTRAL databases from their inception to 4 October 2024 to identify relevant RCTs. Reference lists of included RCTs and previous reviews in this area were hand-searched to identify potentially eligible RCTs. Keywords (title and abstract), Medical Subject Headings (MeSH) terms, and Emtree terms included those for GLP-1 RAs and co-agonists, overweight or obesity, and RCTs. Specific drug names were identified using the PATENTSCOPE database of the World Intellectual Property Organization by searching up the keywords *GLP-1*, *GLP-1/GIP*, *GLP-1/GCG*, and *GLP-1/GCG/GIP* (4). The detailed search strategy is provided in **Supplement Table 1** (available at Annals.org). An adapted search hedge from the Cochrane Handbook for Systematic Reviews of Interventions was used to restrict results to RCTs in MEDLINE and Embase. No language restrictions were used in the search. The RCTs identified by our search were imported into Covidence (Veritas Health Innovation Ltd), a systematic review management software, where duplicates of publications were removed.

Study Selection

The titles and abstracts of identified publications were independently screened for eligibility by 2 authors (A.M. and H.T.) using prespecified inclusion and exclusion criteria. Citations considered to be potentially eligible were retrieved for full-text screening, with discrepancies resolved by consensus or a third reviewer (K.B.F.). Included articles were RCTs that randomly assigned participants to a GLP-1 RA or a co-agonist versus placebo. Trials that randomly assigned patients to other treatment groups in addition to these two were considered eligible. For inclusion, participants needed to be otherwise healthy adults with overweight (body mass index [BMI] ≥27 kg/m^2 and ≥1 weight-related comorbidity) or obesity (BMI ≥30 kg/m^2) and without diabetes. Inclusion was restricted to RCTs with a treatment period of at least 16 weeks; this duration was chosen to account for the dose titration period required for GLP-1 RAs to mitigate gastrointestinal (GI) adverse effects and at least 4 weeks of treatment with a fixed dose (8). Included RCTs had to report change in relative or absolute body weight from baseline to maximum on-treatment follow-up. Trials conducted in people with diabetes or specific patient populations (for example, those with established cardiovascular disease, polycystic ovary syndrome, or chronic obstructive pulmonary disease) were excluded. Trials that enrolled both healthy people and those with diabetes were also excluded; data were not extracted for the healthy subgroup. Abstracts, conference proceedings, observational studies, case reports, case series, editorials, and studies with overlapping patient populations were also excluded.

Data Extraction

Data, including study and baseline participant characteristics and weight loss and safety outcomes, were extracted independently by 2 authors (A.M. and H.T.). Disagreements were resolved by consensus or a third reviewer (K.B.F.). Intention-to-treat analysis data were extracted for all outcomes where possible. Covidence was used for all screening and data extraction.

Outcomes

Our predetermined primary outcome was change in relative or absolute body weight from baseline to maximum follow-up. Prespecified secondary outcomes were changes in BMI, waist circumference, systolic blood pressure (SBP), and diastolic blood pressure (DBP), all reported from baseline to maximum follow-up. At the request of the editors, our primary and secondary outcomes were revised from our original protocol to assess change from baseline to the longest on-treatment follow-up rather than maximum follow-up to focus on on-treatment effects. Safety outcomes included death, serious adverse events (SAEs; overall and the individual end points of severe GI events, biliary disorders [cholecystitis and cholelithiasis], pancreatitis, and psychiatric disorders), any adverse events (AEs), and GI AEs.

Quality Assessment

Risk of bias for included RCTs was assessed independently by 2 reviewers (A.M. and H.T.) using version 2 of the Cochrane Collaboration's tool for assessing risk of bias in randomized trials (RoB 2) (9), with disagreements resolved by consensus. The RoB 2 tool provides an overall structured assessment of the quality of a randomized trial using 5 domains (randomization process, deviations from intended interventions, missing outcome data, measurement of outcome, and selection of reported result). The overall quality of an RCT was determined by its worst domain. Two separate quality assessments were conducted to assess weight loss and AEs. All eligible RCTs were included in our systematic review regardless of their quality.

Role of the Funding Source

The funding sources had no involvement in the conduct of the study, interpretation of the results, or preparation of this manuscript for publication.

RESULTS

Search Results

A total of 5152 records were screened, and 76 were retrieved for full-text review (**Supplement Figure 1**, available at Annals.org). Of these, 26 RCTs (15 491

participants) met our inclusion criteria and were included in our systematic review (10–35).

RCT and Intervention Characteristics

A total of 12 agents were included (Table 1; Supplement Table 2, available at Annals.org), 3 of which are currently commercially available and approved for long-term weight management (liraglutide, semaglutide, and tirzepatide). One agent (exenatide) is commercially available and approved for treatment of type 2 diabetes but not for weight management. Seven agents are single agonists of the GLP-1 pathway (liraglutide, semaglutide, beinaglutide, efpeglenatide, exenatide, noiiglutide, and orforglipron). Four agents are dual agonists, 1 of the GLP-1 and GIP pathways (tirzepatide) and 3 of the GLP-1 and GCG pathways (JNJ-64565111, mazdutide, and survodutide). One agent is a triple agonist of the GLP-1, GIP, and GCG pathways (retatrutide). Of the 26 RCTs, 23 studied subcutaneous agents and 3 studied oral agents. The 2 oral preparations were semaglutide, 50 mg, and orforglipron, 12 to 45 mg. All RCTs were published between 2010 and 2024. Treatment periods ranged from 16 to 104 weeks, with a median of 43 weeks.

Lifestyle Interventions

The majority of RCTs included co-interventions with exercise and diet, although these co-interventions varied across RCTs (Supplement Table 3, available at Annals.org). These interventions were applied to both active and control groups as a form of "background therapy," providing a standard level of lifestyle modification to all participants. However, the specific content and intensity of these co-interventions varied substantially among RCTs, with some prescribing exact caloric deficits and others offering more generalized behavioral advice (Table 1). These differences in lifestyle intervention protocols across RCTs may have influenced the outcomes, particularly in terms of weight loss and metabolic improvements.

Baseline Clinical and Demographic Characteristics

There were 15 491 participants across the 26 RCTs, with 3510 randomly assigned to liraglutide, 3247 to semaglutide, 1896 to tirzepatide, 286 to beinaglutide, 235 to efpeglenatide, 114 to exenatide, 192 to noiiglutide, 222 to orforglipron, 295 to JNJ-64565111, 186 to mazdutide, 345 to survodutide, 268 to retatrutide, and 4695 to placebo (Supplement Table 4, available at Annals.org). The majority of participants were female (72%), and the mean age ranged from 34 to 57 years across RCTs. The mean body weight of participants at baseline ranged from 87 to 115 kg and the mean BMI of participants ranged from 30 to 41 kg/m^2 across RCTs. The mean waist circumference ranged from 102 to 121 cm. Mean SBPs ranged from 116 to 132 mm Hg, and mean DBPs ranged from 76 to 84 mm Hg.

Quality Assessment

Weight Loss Outcomes

A total of 22 RCTs had low overall risk of bias per the RoB 2 tool, 3 ($n = 766$) had some concerns (11, 20, 28), and 1 had high risk of bias (27). Concerns were present in the RCT by Basolo and colleagues (27) due to missing outcome data, as follow-up data were available for only 13 of 41 participants (31.7%) in the exenatide group and 20 of 39 (51.2%) in the placebo group at maximum follow-up. The RCT by Neeland and colleagues (11) also had concerns about bias due to missing outcome data, as only 128 of 185 participants (69.2%) were included in the final analysis. The RCT by Rosenstock and colleagues (28) had concerns about bias arising from the randomization process as they did not report any baseline characteristics and due to deviations from their intended intervention as the RCT was single-blinded. Finally, the RCT by Rubino and colleagues (20) had some concerns about bias in selection of the reported outcome as their daily and weekly placebo groups were pooled in their results, which made the comparability of daily placebo versus the weekly active intervention unclear. A summary of the RoB 2 results stratified by risk domain for the outcome of weight loss is shown in Supplement Figure 2 (available at Annals.org).

Safety Outcomes

Our quality assessment for the outcome of AEs revealed that all 26 RCTs had some concerns related to measurement of the outcome. These concerns were due to either a lack of information on how AEs were assessed or the use of self-reporting for many of the AEs. In RCTs that reported how AEs were collected, laboratory tests (hematology, clinical chemistry, or urinalysis), physical examinations (electrocardiography, radiologic scans, or vital sign measurements), and self-reporting by participants were used. Specifically, GI AEs were largely assessed through self-report, which may have introduced some bias as participants could have underreported the frequency or severity of symptoms (36). All RCTs were at low risk of bias related to the selection of reported results as all reported overall occurrence of AEs. However, the reporting of specific AEs of interest varied across RCTs. A summary of the RoB 2 results stratified by risk domain for the outcome of AEs is provided in Supplement Figure 3 (available at Annals.org).

Weight Loss

Across all RCTs, the use of a GLP-1 RA or co-agonist was associated with decreased relative and absolute body weight compared with placebo. The magnitude of weight loss varied across agents, with the largest reductions observed in RCTs evaluating retatrutide and tirzepatide. Point estimates and measures of variability are presented in Tables 2 and 3, and treatment differences between the GLP-1 RA and placebo groups are

Table 1. Characteristics of Randomized Controlled Trials of GLP-1 RAs Versus Placebo for Weight Loss in People Without Diabetes

Trial, Year (Reference); Trial Phase	Location	Population	Sample Size, *n*	Active Groups	Additional Group	Lifestyle Interventions	Treatment Period, *wk*
Liraglutide (GLP-1 RA)							
Maselli et al, 2022 (10); phase 2	United States	Aged 18–65 y with obesity; residing within 125 miles of center	136	Once-daily subcutaneous, 3.0 mg	–	Behavioral counseling without prescription	16
Neeland et al, 2021 (11); phase 4	United States	Aged ≥35 y with obesity or overweight	185	Once-daily subcutaneous, 3.0 mg	–	Prescribed 500-kcal deficit and ≥150 min of exercise per week	40
Astrup et al, 2012 (12); phase 3	8 countries	Aged 18–65 y with stable weight, BMI of 30–40 kg/m^2, and fasting plasma glucose level <7 mmol/L (<126 mg/dL) at run-in	564	Once-daily subcutaneous, 1.2 mg, 1.8 mg, 2.4 mg, or 3.0 mg	Thrice-daily oral orlistat, 120 mg	Prescribed 500-kcal deficit	52
Pi-Sunyer et al, 2015 (13); phase 3	27 countries	Aged ≥18 y with stable weight and overweight or obesity	3731	Once-daily subcutaneous, 3.0 mg	–	Prescribed 500-kcal deficit and ≥150 min of exercise per week	56
Wadden et al, 2020 (14); phase 3b	United States	Aged ≥18 y with stable weight (≤5-kg change within 90 d of screening) and obesity	282	Once-daily subcutaneous, 3.0 mg	–	Prescribed diet and exercise individualized to patient	56
Semaglutide (GLP-1 RA)							
Friedrichsen et al, 2021 (15); phase 1	Germany	Aged 18–65 y with BMI of 30–45 kg/m^2	72	Once-weekly subcutaneous, 2.4 mg	–	Maintenance of usual diet and physical activity	20
Gabe et al, 2024 (16); phase 1	Germany	Aged 18–65 y with BMI of 30–45 kg/m^2	61	Once-daily oral, 50 mg	–	Maintenance of usual diet and physical activity	20
O'Neil et al, 2018 (17); phase 2	8 countries	Aged ≥18 y with obesity from nonendocrine cause and self-reported weight loss effort	957	Once-daily subcutaneous, 0.05 mg, 0.1 mg, 0.2 mg, 0.3 mg, or 0.4 mg	Once-daily subcutaneous liraglutide, 3.0 mg	Prescribed 500-kcal deficit and ≥150 min of exercise per week	52
McGowan et al, 2024 (18); phase 3	Canada, Denmark, Finland, Spain, United Kingdom	Aged ≥18 y with BMI of 30 kg/m^2 and prediabetes (hemoglobin A_{1c} level of 6%–6.4% or fasting plasma glucose level of 5.5–6.9 mmol/L at screening)	207	Once-weekly subcutaneous, 2.4 mg	–	Behavioral counseling without prescription	52
Knop et al, 2023 (19); phase 3	9 countries	Aged ≥18 y (≥20 y in Japan) with overweight or obesity and self-reported diet weight loss effort	667	Once-daily oral, 50 mg	–	Prescribed 500-kcal deficit and ≥150 min of exercise per week	68
Rubino et al, 2022 (20); phase 3	United States	Aged ≥18 y with overweight or obesity and self-reported diet weight loss effort	338	Once-weekly subcutaneous, 2.4 mg	Once-daily subcutaneous liraglutide, 3.0 mg	Prescribed 500-kcal deficit and ≥150 min of exercise per week	68

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Table 1–Continued

Trial, Year (Reference); Trial Phase	Location	Population	Sample Size, *n*	Active Groups	Additional Group	Lifestyle Interventions	Treatment Period, *wk*
Wadden et al, 2021 (21); phase 3	United States	Aged ≥18 y with overweight or obesity and self-reported diet weight loss effort	611	Once-weekly subcutaneous, 2.4 mg	–	Prescribed diet and exercise individualized to patient	68
Wilding et al, 2021 (22); phase 3	17 countries	Aged ≥18 y with overweight or obesity and self-reported diet weight loss effort	1961	Once-weekly subcutaneous, 2.4 mg	–	Prescribed 500-kcal deficit and ≥150 min of exercise per week	68
Garvey et al, 2022 (23); phase 3	Canada, Hungary, Italy, Spain, United States	Aged ≥18 y with overweight or obesity and self-reported diet weight loss effort	304	Once-weekly subcutaneous, 2.4 mg	–	Prescribed 500-kcal deficit and ≥150 min of exercise per week	104
Tirzepatide (dual GLP-1/GIP RA)							
Jastreboff et al, 2022 (24); phase 3	9 countries	Aged ≥18 y with overweight or obesity and unsuccessful diet effort to lose weight	2539	Once-weekly subcutaneous, 5 mg, 10 mg, or 15 mg	–	Prescribed 500-kcal deficit and ≥150 min of exercise per week	72
Beinaglutide (GLP-1 RA)							
Chen et al, 2024 (25); phase 3	China	Aged 18–70 y with BMI ≥28 kg/m^2 or BMI >24–27.9 kg/m^2 and weight-related comorbidities	427	Thrice-daily subcutaneous, 0.2 mg	–	Details of intervention not provided	16
Efpeglenatide (GLP-1 RA)							
Pratley et al, 2019 (26); phase 2	Germany, Hungary, the Netherlands, South Korea, United States	Aged 18–65 y with overweight or obesity, stable health, and fasting plasma glucose level <7 mmol/L (<126 mg/dL)	295	Subcutaneous, 4 mg once weekly, 6 mg once weekly, 6 mg biweekly, or 8 mg biweekly	–	Behavioral counseling without prescription	20
Exenatide (GLP-1 RA)							
Basolo et al, 2018 (27); phase 3	United States	Aged <55 y with obesity and interest in weight loss but stable weight (variation <2.3 kg within past 6 mo)	80	Twice-daily subcutaneous, 10 mcg	–	Behavioral counseling without prescription	24
Rosenstock et al, 2010 (28); phase 2	United States	Adults with obesity and stable weight	152	Twice-daily subcutaneous, 10 mcg	–	Details of intervention not provided	24
Noiiglutide (GLP-1 RA)							
Li et al, 2024 (29); phase 2	China	Aged 18–65 y with BMI of 28–40 kg/m^2; engaged in diet and exercise for ≥3 mo before screening and had <5% weight change	254	Once-daily subcutaneous, 0.12 mg, 0.24 mg, or 0.36 mg	–	Prescribed 500-kcal deficit and ≥150 min of exercise per week	24

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Table 1–Continued

Trial, Year (Reference); Trial Phase	Location	Population	Sample Size, *n*	Active Groups	Additional Group	Lifestyle Interventions	Treatment Period, *wk*
Orforglipron (GLP-1 RA)							
Wharton et al, 2023 (30); phase 2	Hungary, Canada, United States	Aged 18–75 y with overweight or obesity and stable weight (≤5% gain or loss) for the 3 mo before randomization	272	Once-daily oral, 12 mg, 24 mg, 36 mg, or 45 mg	–	Behavioral counseling without prescription	36
JNJ-64565111 (dual GLP-1/GCG RA)							
Alba et al, 2021 (31); phase 2	United States	Aged 18–70 y with BMI of 35–50 kg/m^2 and stable weight (≤5% change within 12 wk before screening)	474	Once-weekly subcutaneous, 5.0 mg, 7.4 mg, or 10 mg	Once-daily subcutaneous liraglutide, 3.0 mg	Prescribed 600-kcal deficit	26
Mazdutide (dual GLP-1/GCG RA)							
Ji et al, 2023 (32); phase 2	China	Aged 18–75 y with BMI of 30–50 kg/m^2 or BMI of 27–<30 kg/m^2 with ≥1 weight-related condition	248	Once-weekly subcutaneous, 3 mg, 4.5 mg, or 6 mg	–	Maintenance of usual diet and physical activity	24
Survodutide (BI 456906) (dual GLP-1/GCG RA)							
Jungnik et al, 2023 (33); phase 1	Germany	Aged 18–70 y with BMI of 27–40 kg/m^2 and stable weight (≤5% change within 3 mo before screening) of ≥70 kg (females) or ≥80 kg (males)	45	Subcutaneous, 2.4 mg once weekly, 4.8 mg once weekly, or 4.8 mg twice weekly	–	Details of intervention not provided	16
le Roux et al, 2024 (34); phase 2	12 countries	Aged 18–75 y with BMI >27 kg/m^2 and stable weight of ≥70 kg (females) or ≥80 kg (males)	386	Once-weekly subcutaneous, 0.6 mg, 2.4 mg, 3.6 mg, or 4.8 mg	–	Prescribed 500-kcal deficit and ≥150 min of exercise per week	46
Retatrutide (triple GLP-1/GIP/GCG RA)							
Jastreboff et al, 2023 (35); phase 2	United States	Aged 18–75 y with overweight or obesity	338	Once-weekly subcutaneous, 1 mg, 4 mg, 8 mg or 12 mg	–	Behavioral counseling without prescription	48

BMI = body mass index; GCG = glucagon; GIP = glucose-dependent insulinotropic polypeptide; GLP-1 RA = glucagon-like peptide-1 receptor agonist.

Table 2. Change in Efficacy Outcomes in Trials of FDA-Approved GLP-1 RAs for Weight Loss*

Trial	Treatment Duration, *wk*	Change in Weight, %	Change in Weight, *kg*	Change in BMI, *kg/m²*	Change in Waist Circumference, *cm*	Change in Systolic Blood Pressure, *mm Hg*	Change in Diastolic Blood Pressure, *mm Hg*
Liraglutide							
Maselli et al, 2022 (10)							
Liraglutide, 3.0 mg sq qd	16	–	−5.8 (−8.3 to −3.9)†	–	–	–	–
Placebo	16	–	0.0 (−3.1 to −2.1)†	–	–	–	–
Alba et al, 2021 (31)							
Liraglutide, 3.0 mg sq qd	26	−7.5 ± 0.5	–	–	–	−0.8 ± NR	−0.4 ± NR
Placebo	26	−1.8 ± 0.7	–	–	–	0.0 ± NR	−0.1 ± NR
Neeland et al, 2021 (11)‡							
Liraglutide, 3.0 mg sq qd	40	−6.59 (4.80)§	−6.75 (5.35)§	−2.46 (2.01)§	−7.40 (6.82)§	–	–
Placebo	40	−1.19 (4.68)§	−1.30 (4.79)§	−0.43 (1.86)§	−4.60 (6.69)§	–	–
Astrup et al, 2012 (12)							
Liraglutide, 1.2 mg sq qd	52	–	−3.8 ± NR	–	−4.5 ± NR	−4.2 ± NR	−1.7 ± NR
Liraglutide, 1.8 mg sq qd	52	–	−5.4 ± NR	–	−5.2 ± NR	−4.0 ± NR	−1.2 ± NR
Liraglutide, 2.4 mg sq qd	52	–	−6.1 ± NR	–	−6.5 ± NR	−7.0 ± NR	−1.5 ± NR
Liraglutide, 3.0 mg sq qd	52	–	−7.8 ± NR	–	−7.8 ± NR	−4.9 ± NR	−2.8 ± NR
Placebo	52	–	−2.0 ± NR	–	−3.0 ± NR	−1.6 ± NR	−0.2 ± NR
O'Neil et al, 2018 (17)‖							
Liraglutide, 3.0 mg sq qd	52	−7.8 ± 0.85	−8.47 ± 0.93	−3.03 ± 0.33	−8.35 ± 0.89	−5.45 ± 1.18	−2.70 ± 0.82
Placebo	52	−2.3 ± 0.74	−2.48 ± 0.82	−0.88 ± 0.29	−3.47 ± 0.81	−1.58 ± 1.04	−1.50 ± 0.73
Pi-Sunyer et al, 2015 (13)							
Liraglutide, 3.0 mg sq qd	56	−8.0 (6.7)§	−8.4 (7.3)§	−3.0 (2.6)§	−8.2 (7.3)§	−4.2 (12.2)§	−2.6 (8.7)§
Placebo	56	−2.6 (5.7)§	−2.8 (6.5)§	−1.0 (2.3)§	−3.9 (6.6)§	−1.5 (12.4)§	−1.9 (8.7)§
Wadden et al, 2020 (14)							
Liraglutide, 3.0 mg sq qd	56	−7.5 ± NR	–	–	−9.4 ± NR	−2.8 ± NR	−1.0 ± NR
Placebo	56	−4.0 ± NR	–	–	−6.7 ± NR	−0.6 ± NR	−0.8 ± NR
Rubino et al, 2022 (20)‡‖							
Liraglutide, 3.0 mg sq qd	68	−6.4 (−8.2 to −4.6)	−6.8 (−8.8 to −4.9)	–	−6.6 (−8.3 to −4.9)	−2.9 (−5.3 to −0.5)	−0.5 (−2.3 to 1.3)
Placebo	68	−1.9 (−4.0 to 0.2)	−1.6 (−3.9 to 0.8)	–	−2.0 (−4.0 to 0.1)	3.2 (0.3 to 6.1)	0.7 (−1.5 to 2.9)
Semaglutide							
Friedrichsen et al, 2021 (15)							
Semaglutide, 2.4 mg sq qw	20	−9.9 (NR)§	−10.4 (6.3)§	–	–	–	–
Placebo	20	−0.4 (NR)§	−0.4 (2.6)§	–	–	–	–
Gabe et al, 2024 (16)							
Semaglutide, 50 mg po qd	20	−9.8 ± 3.8	−10.1 ± 4.1	–	–	–	–
Placebo	20	−1.5 ± 3.8	−1.6 ± 3.9	–	–	–	–
O'Neil et al, 2018 (17)‖							
Semaglutide, 0.05 mg sq qd	52	−6.0 ± 0.85	−6.66 ± 0.94	−2.37 ± 0.33	−6.11 ± 0.93	−4.46 ± 1.20	−2.55 ± 0.84
Semaglutide, 0.1 mg sq qd	52	−8.6 ± NR	−9.34 ± 0.93	−3.36 ± 0.33	−8.75 ± 0.90	−5.76 ± 1.18	−2.65 ± 0.82
Semaglutide, 0.2 mg sq qd	52	−11.6 ± NR	−12.30 ± 0.93	−4.38 ± 0.33	−11.02 ± 0.89	−6.26 ± 1.19	−4.09 ± 0.83
Semaglutide, 0.3 mg sq qd	52	−11.2 ± NR	−12.45 ± 0.93	−4.40 ± 0.33	−10.91 ± 0.89	−6.41 ± 1.19	−2.98 ± 0.83
Semaglutide, 0.3 mg sq qd FE¶	52	−11.4 ± 0.85	−12.54 ± 0.93	−4.48 ± 0.33	−11.06 ± 0.95	−6.07 ± 1.19	−2.20 ± 0.83

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Table 2–Continued

Trial	Treatment Duration, *wk*	Change in Weight, %	Change in Weight, *kg*	Change in BMI, *kg/m²*	Change in Waist Circumference, *cm*	Change in Systolic Blood Pressure, *mm Hg*	Change in Diastolic Blood Pressure, *mm Hg*
Semaglutide, 0.4 mg sq qd	52	−13.8 ± 0.83	−15.15 ± 0.92	−5.40 ± 0.33	−12.31 ± 0.91	−5.81 ± 1.16	−3.61 ± 0.80
Semaglutide, 0.4 mg sq qd FE¶	52	−16.3 ± 0.83	−17.36 ± 0.92	−6.21 ± 0.33	−14.88 ± 0.88	−10.26 ± 1.16	−5.52 ± 0.80
Placebo	52	−2.3 ± 0.74	−2.48 ± 0.82	−0.88 ± 0.29	−3.47 ± 0.81	−1.58 ± 1.04	−1.50 ± 0.73
McGowan et al, 2024 (18)							
Semaglutide, 2.4 mg sq qw	52	−13.9 ± 0.7	−15.2 ± 0.8	–	−11.1 ± 0.8	−8.8 ± 1.1	–
Placebo	52	−2.7 ± 0.6	−2.8 ± 0.6	–	−2.8 ± 0.7	−1.0 ± 1.4	–
Knop et al, 2023 (19)							
Semaglutide, 50 mg po qd	68	−15.1 ± 0.5	−15.5 ± 0.5	−5.6 ± 0.2	−13.0 ± 0.5	−6.6 ± 0.7	−2.4 ± 0.5
Placebo	68	−2.4 ± 0.5	−2.5 ± 0.5	−0.9 ± 0.2	−3.0 ± 0.5	−0.3 ± 0.5	−0.6 ± 0.5
Rubino et al, 2022 (20)‡‖							
Semaglutide, 2.4 mg sq qw	68	−15.8 (−17.6 to −13.9)	−15.3 (−17.3 to −13.4)	–	−13.2 (−15.0 to −11.5)	−5.7 (−8.1 to −3.3)	−5.0 (−7.0 to −3.1)
Placebo	68	−1.9 (−4.0 to 0.2)	−1.6 (−3.9 to 0.8)	–	−2.0 (−4.0 to 0.1)	3.2 (0.3 to 6.1)	0.7 (−1.5 to 2.9)
Wadden et al, 2021 (21)							
Semaglutide, 2.4 mg sq qw	68	−16.0 ± NR	−16.8 ± NR	−6.0 ± NR	−14.6 ± NR	−5.6 ± NR	−3.0 ± NR
Placebo	68	−5.7 ± NR	−6.2 ± NR	−2.2 ± NR	−6.3 ± NR	−1.6 ± NR	−0.8 ± NR
Wilding et al, 2021 (22)							
Semaglutide, 2.4 mg sq qw	68	−14.85 ± NR	−15.3 ± NR	−5.54 ± NR	−13.54 ± NR	−6.16 ± NR	−2.83 ± NR
Placebo	68	−2.41 ± NR	−2.6 ± NR	−0.92 ± NR	−4.13 ± NR	−1.06 ± NR	−0.42 ± NR
Garvey et al, 2022 (23)							
Semaglutide, 2.4 mg sq qw	104	−15.2 ± 0.9	−16.1 ± 1.0	−5.9 ± 0.4	−14.4 ± 0.9	−5.7 ± 1.1	−4.4 ± 0.9
Placebo	104	−2.6 ± 1.1	−3.2 ± 1.2	−1.6 ± 0.6	−5.2 ± 1.2	−1.6 ± 1.2	−0.8 ± 0.9
Tirzepatide							
Jastreboff et al, 2022 (24)							
Tirzepatide, 5 mg sq qw	72	−15.0 (−15.9 to −14.2)	−16.1 ± NR	–	−14.0 (−14.9 to −13.1)	−7.0 (−7.9 to −6.1)	−5.2 (−5.8 to −4.6)
Tirzepatide, 10 mg sq qw	72	−19.5 (−20.4 to −18.5)	−22.2 ± NR	–	−17.7 (−18.7 to −16.8)	−8.2 (−9.1 to −7.3)	−5.5 (−6.1 to −4.9)
Tirzepatide, 15 mg sq qw	72	−20.9 (−21.8 to −19.9)	−23.6 ± NR	–	−18.5 (−19.3 to −17.6)	−7.6 (−8.5 to −6.7)	−4.6 (−5.2 to −4.0)
Placebo	72	−3.1 (−4.3 to −1.9)	−2.4 ± NR	–	−4.0 (−5.1 to −2.8)	−1.2 (−2.1 to −0.3)	−1.0 (−1.7 to −0.3)

BMI = body mass index; FDA = U.S. Food and Drug Administration; FE = fast dose escalation; GLP-1 RA = glucagon-like peptide-1 receptor agonist; NR = not reported; po = oral; qd = once daily; qw = once weekly; sq = subcutaneous.
* Data are means ± SEs or means (95% CIs) unless otherwise indicated.
† Data are medians (IQRs).
‡ Study with some concerns or high risk of bias for the outcome of weight loss.
§ Data are means (SDs).
‖ Study is reported twice because it included 2 active groups.
¶ Study included 2 groups receiving the same dose with varying uptitration schedules.

presented in the Figure and in Supplement Figure 4 (available at Annals.org).

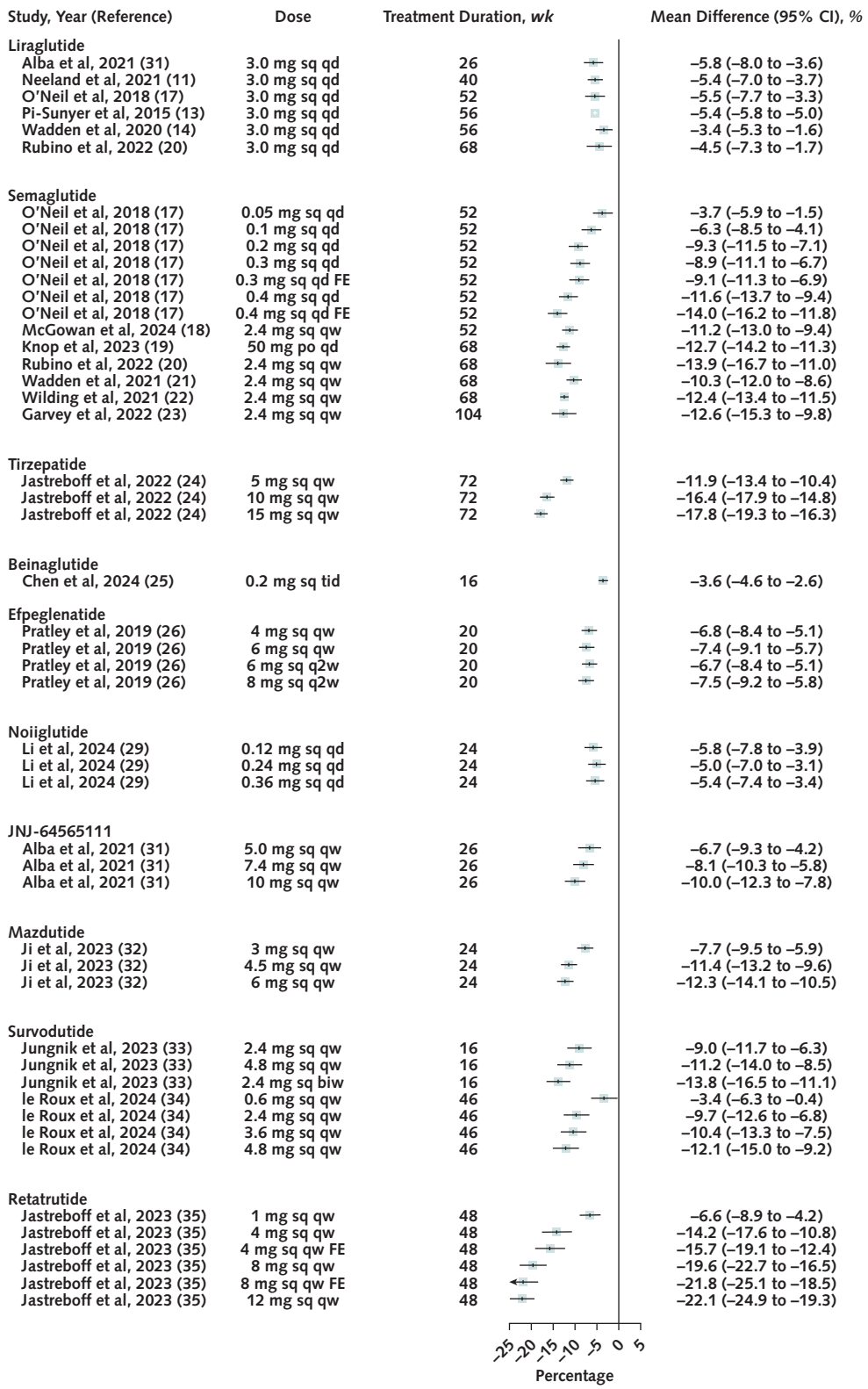
Commercially Available Agents

Among the available therapies for weight management (Table 2 and Figure), the most pronounced effect was reported in an RCT of tirzepatide, 15 mg (−17.8% [95% CI, −19.3% to −16.3%]). Trials of semaglutide reported weight losses of up to −13.9% (CI, −16.7% to −11.0%) with a 2.4-mg subcutaneous dose and up to −12.7% (CI, −14.2% to −11.3%) with a 50-mg oral dose after 68 weeks of therapy. Use of liraglutide in RCTs yielded more moderate weight reductions of up to −5.8% (CI, −8.0% to −3.6%).

Premarket Agents

Of the 9 agents that are not yet commercially available for weight management (Table 3 and Figure), the greatest placebo-subtracted reduction in mean body weight was observed in an RCT of the triple agonist

Figure. Forest plot of mean differences in relative body weight change with use of GLP-1 RAs versus placebo.



Nineteen of 26 RCTs and 10 of 12 agents are reported due to missing 95% CIs for the difference in change from baseline. biw = twice weekly; FE = fast dose escalation; GLP-1 RA = glucagon-like peptide-1 receptor agonist; po = oral; q2w = biweekly; qd = once daily; qw = once weekly; RCT = randomized controlled trial; sq = subcutaneous; tid = thrice daily.

Table 3. Change in Efficacy Outcomes in Trials of Premarket GLP-1 RAs for Weight Loss*

Trial	Treatment Duration, *wk*	Change in Weight, %	Change in Weight, *kg*	Change in BMI, *kg/m²*	Change in Waist Circumference, *cm*	Change in Systolic Blood Pressure, *mm Hg*	Change in Diastolic Blood Pressure, *mm Hg*
Beinaglutide							
Chen et al, 2024 (25)							
Beinaglutide, 0.2 mg sq tid	16	−6.0 ± 0.4	−6.62 (3.74)†	–	−4.91 ± 0.38	−2.60 ± 0.58	−1.80 ± 0.46
Placebo	16	−2.4 ± 0.5	−3.73 (3.18)†	–	−3.11 ± 0.51	−1.60 ± 0.78	−1.40 ± 0.61
Efpeglenatide							
Pratley et al, 2019 (26)							
Efpeglenatide, 4 mg sq qw	20	−6.7 ± 0.6	−6.6 ± 0.6	−2.4 ± 0.2	−5.2 ± 1.0	−3.5 ± 1.4	−0.1 ± 0.9
Efpeglenatide, 6 mg sq qw	20	−7.3 ± 0.6	−7.3 ± 0.6	−2.6 ± 0.2	−6.7 ± 1.0	−6.1 ± 1.4	−1.3 ± 0.9
Efpeglenatide, 6 mg sq q2w	20	−6.7 ± 0.6	−6.4 ± 0.6	−2.3 ± 0.2	−6.2 ± 1.0	−0.3 ± 1.4	1.8 ± 0.9
Efpeglenatide, 8 mg sq q2w	20	−7.4 ± 0.6	−7.1 ± 0.6	−2.6 ± 0.2	−8.3 ± 1.0	−3.0 ± 1.4	−0.3 ± 0.9
Placebo	20	0.1 ± 0.6	−0.1 ± 0.6	0.0 ± 0.2	−0.9 ± 1.0	−0.1 ± 1.3	0.1 ± 0.9
Exenatide							
Basolo et al, 2018 (27)‡							
Exenatide, 10 mcg sq bid	24	–	–	–	–	–	–
Placebo	24	–	–	–	–	–	–
Treatment difference	–	–	−1.72 (−5.77 to 2.30)	–	–	–	–
Rosenstock et al, 2010 (28)‡							
Exenatide, 10 mcg sq bid	24	–	−5.1 ± 0.5	–	–	–	–
Placebo	24	–	−1.6 ± 0.5	–	–	–	–
Noiiglutide							
Li et al, 2024 (29)							
Noiiglutide, 0.12 mg sq qd	24	−9.80 (−11.18 to −8.43)	−8.50 (−9.74 to −7.27)	−3.13 (−3.57 to −2.68)	−8.57 (−10.05 to −7.10)	−6.68 (−8.87 to −4.49)	−5.05 (−6.60 to −3.50)
Noiiglutide, 0.24 mg sq qd	24	−9.01 (−10.40 to −7.62)	−8.03 (−9.28 to −6.79)	−2.93 (−3.38 to −2.48)	−6.85 (−8.34 to −5.36)	−4.42 (−6.69 to −2.15)	−2.81 (−4.42 to −1.20)
Noiiglutide, 0.36 mg sq qd	24	−9.39 (−10.80 to −7.97)	−8.26 (−9.53 to −6.99)	−3.04 (−3.50 to −2.58)	−6.74 (−8.26 to −5.23)	−5.27 (−7.58 to −2.96)	−3.18 (−4.81 to −1.55)
Placebo	24	−3.97 (−5.39 to −2.56)	−3.65 (−4.92 to −2.37)	−1.26 (−1.72 to −0.80)	−3.54 (−5.05 to −2.03)	−1.18 (−3.49 to 1.13)	−2.74 (−4.38 to −1.11)
Orforglipron							
Wharton et al, 2023 (30)							
Orforglipron, 12 mg po qd	36	−9.4 (−11.5 to −7.4)	−9.8 (−11.9 to −7.6)	−3.4 (−4.2 to −2.7)	−9.6 (−11.9 to −7.3)	–	–
Orforglipron, 24 mg po qd	36	−12.5 (−14.5 to −10.5)	−13.6 (−15.7 to −11.6)	−4.7 (−5.4 to −4.0)	−11.2 (−13.4 to −8.9)	–	–
Orforglipron, 36 mg po qd	36	−13.5 (−15.3 to −11.6)	−14.2 (−16.2 to −12.3)	−5.0 (−5.7 to −4.4)	−10.6 (−12.7 to −8.5)	–	–
Orforglipron, 45 mg po qd	36	−14.7 (−16.5 to −12.8)	−15.4 (−17.4 to −13.5)	−5.5 (−6.1 to −4.8)	−13.6 (−15.7 to −11.5)	–	–
Placebo	36	−2.3 (−4.3 to −0.4)	−2.4 (−4.5 to −0.4)	−0.9 (−1.6 to −0.2)	−4.0 (−6.2 to −1.8)	–	–
JNJ-64565111							
Alba et al, 2021 (31)							
JNJ-64565111, 5.0 mg sq qw	26	−8.5 ± 0.8	–	–	–	−6.4 ± NR	−2.7 ± NR
JNJ-64565111, 7.4 mg sq qw	26	−9.8 ± 0.6	–	–	–	−9.5 ± NR	−4.0 ± NR
JNJ-64565111, 10 mg sq qw	26	−11.8 ± 0.6	–	–	–	−7.6 ± NR	−4.1 ± NR
Placebo	26	−1.8 ± 0.7	–	–	–	0.0 ± NR	−0.1 ± NR

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Table 3–Continued

Trial	Treatment Duration, *wk*	Change in Weight, %	Change in Weight, *kg*	Change in BMI, *kg/m²*	Change in Waist Circumference, *cm*	Change in Systolic Blood Pressure, *mm Hg*	Change in Diastolic Blood Pressure, *mm Hg*
Mazdutide							
Ji et al, 2023 (32)							
Mazdutide, 3 mg sq qw	24	−6.7 ± 0.7	−6.4 ± 0.6	−2.3 ± 0.2	−5.6 ± 0.7	−1.3 ± 1.3	−0.6 ± 0.8
Mazdutide, 4.5 mg sq qw	24	−10.4 ± 0.7	−9.1 ± 0.6	−3.3 ± 0.2	−8.5 ± 0.7	−2.2 ± 1.2	−1.7 ± 0.8
Mazdutide, 6 mg sq qw	24	−11.3 ± 0.7	−9.9 ± 0.6	−3.6 ± 0.2	−8.8 ± 0.7	−6.9 ± 1.2	−3.6 ± 0.8
Placebo	24	1.0 ± 0.7	1.1 ± 0.6	0.4 ± 0.2	−1.1 ± 0.7	2.9 ± 1.2	0.9 ± 0.8
Survodutide (BI 456906)							
Jungnik et al, 2023 (33)							
Survodutide, 2.4 mg sq qw	16	−9.31 ± 1.03	–	–	–	–	–
Survodutide, 4.8 mg sq qw	16	−11.50 ± 1.10	–	–	–	–	–
Survodutide, 2.4 mg sq biw	16	−14.10 ± 1.05	–	–	–	–	–
Placebo	16	−0.27 ± 1.22	–	–	–	–	–
le Roux et al, 2024 (34)							
Survodutide, 0.6 mg sq qw	46	−6.2 (−8.3 to −4.1)	−7.2 (−9.3 to −5.1)	−2.8 (2.2)†	−8.3 (−10.7 to −5.9)	−6.2 (−9.1 to −3.3)	−3.3 (−5.1 to −1.5)
Survodutide, 2.4 mg sq qw	46	−12.5 (−14.5 to −10.5)	−14.8 (−16.8 to −12.7)	−6.0 (2.8)†	−15.0 (−17.4 to −12.6)	−8.1 (−11.0 to −5.2)	−4.4 (−6.1 to −2.6)
Survodutide, 3.6 mg sq qw	46	−13.2 (−15.3 to −11.2)	−15.6 (−17.7 to −13.6)	−6.1 (3.1)†	−15.0 (−17.3 to −12.6)	−8.7 (−11.5 to −5.8)	−4.3 (−6.0 to −2.6)
Survodutide, 4.8 mg sq qw	46	−14.9 (−16.9 to −13.0)	−18.5 (−20.5 to −16.4)	−7.0 (3.2)†	−16.0 (−18.4 to −13.7)	−8.6 (−11.5 to −5.7)	−4.8 (−6.6 to −3.1)
Placebo	46	−2.8 (−4.9 to −0.7)	−2.7 (−4.7 to −0.6)	−1.1 (2.0)†	−4.0 (−6.3 to −1.6)	−2.5 (−5.3 to −0.4)	−1.9 (−3.6 to −0.1)
Retatrutide							
Jastreboff et al, 2023 (35)							
Retatrutide, 1 mg sq qw	48	−8.7 (−10.5 to −6.8)	−9.4 (−11.4 to −7.3)	−3.2 (−3.9 to −2.5)	−6.5 (−8.7 to −4.3)	−3.0 ± NR	−1.3 ± NR
Retatrutide, 4 mg sq qw	48	−16.3 (−19.4 to −13.2)	−17.3 (−20.8 to −13.8)	−6.1 (−7.4 to −4.9)	−14.6 (−17.6 to −11.5)	−8.3 ± NR	−4.6 ± NR
Retatrutide, 4 mg sq qw FE§	48	−17.8 (−20.8 to −14.8)	−19.1 (−22.7 to −15.6)	−6.7 (−7.8 to −5.5)	−14.9 (−18.2 to −11.5)	−10.1 ± NR	−4.7 ± NR
Retatrutide, 8 mg sq qw	48	−21.7 (−24.5 to −19.0)	−23.5 (−26.7 to −20.4)	−8.1 (−9.2 to −7.0)	−18.5 (−21.4 to −15.7)	−10.8 ± NR	−8.1 ± NR
Retatrutide, 8 mg sq qw FE§	48	−23.9 (−26.8 to −20.9)	−25.9 (−29.2 to −22.6)	−9.0 (−10.1 to −7.9)	−18.5 (−21.5 to −15.5)	−12.1 ± NR	−6.7 ± NR
Retatrutide, 12 mg sq qw	48	−24.2 (−26.6 to −21.8)	−26.2 (−28.8 to −23.6)	−9.1 (−10.0 to −8.2)	−19.6 (−22.1 to −17.1)	−11 ± NR	−5.1 ± NR
Placebo	48	−2.1 (−3.5 to −0.7)	−1.8 (−3.5 to −0.2)	−0.7 (−1.3 to −0.2)	−2.6 (−4.6 to −0.7)	−2.3 ± NR	−0.7 ± NR

bid = twice daily; biw = twice weekly; BMI = body mass index; FE = fast dose escalation; GLP-1 RA = glucagon-like peptide-1 receptor agonist; NR = not reported; po = oral; q2w = biweekly; qd = once daily; qw = once weekly; sq = subcutaneous; tid = thrice daily.
* Data are means ± SEs or means (95% CIs) unless otherwise indicated.
† Data are means (SDs).
‡ Study with some concerns or high risk of bias for the outcome of weight loss.
§ Study included 2 groups receiving the same dose with varying uptitration schedules.

retatrutide, 12 mg (−22.1% [CI, −24.9% to −19.3%]). Other agents, such as orforglipron (oral single GLP-1 agonist), mazdutide, and survodutide (both subcutaneous dual GLP-1 and GCG agonists), were also efficacious to varying degrees. Several RCTs of single GLP-1 agonists, such as beinaglutide, exenatide, and noiiglutide, showed smaller reductions.

Cardiovascular Risk Factors

Compared with placebo, the use of a GLP-1 RA or co-agonist was associated with decreased BMI, waist circumference, and blood pressure for all agents (Tables 2 and 3; Supplement Figures 5 to 8, available at Annals.org). Change in BMI was reported in 13 of 26 RCTs, change in waist circumference was reported

Table 4. Pooled Safety Outcomes in Trials of GLP-1 RAs for Weight Loss*

Trial	Treatment Duration, *wk*	Any AE, *n/N (%)*	Gastrointestinal AE, *n/N (%)*	AE Leading to Treatment Discontinuation, *n/N (%)*	Serious AE, *n/N (%)*	Death, *n/N (%)*
Liraglutide						
Maselli et al, 2022 (10)						
Liraglutide, 3.0 mg	16	NR	NR	8/67 (11.9)	NR	NR
Placebo	16	NR	NR	1/69 (2.4)	NR	NR
Alba et al, 2021 (31)†						
Liraglutide, 3.0 mg	26	96/119 (80.7)	71/119 (59.7)	20/119 (16.8)	4/119 (3.4)	1/119 (0.8)
Placebo	26	43/60 (71.7)	17/60 (28.3)	0/60 (0.0)	4/60 (6.7)	0/60 (0.0)
Neeland et al, 2021 (11)						
Liraglutide, 3.0 mg	40	NR	43/92 (46.7)	0/92 (0.0)	0/92 (0.0)	0/92 (0.0)
Placebo	40	NR	12/93 (12.9)	8/93 (8.6)	0/93 (0.0)	0/93 (0.0)
Astrup et al, 2012 (12)						
Liraglutide, 1.2–3.0 mg	52	349/371 (94.1)	251/371 (67.7)	30/371 (8.1)	20/371 (5.4)	0/371 (0.0)
Placebo	52	87/98 (88.8)	37/98 (37.8)	3/98 (3.1)	3/98 (3.1)	0/98 (0.0)
O'Neil et al, 2018 (17)†						
Liraglutide, 3.0 mg	52	88/103 (85.4)	77/103 (74.8)	9/103 (8.7)	4/103 (3.9)	0/103 (0.0)
Placebo	52	107/136 (78.7)	52/136 (38.2)	4/136 (2.9)	11/136 (8.1)	0/136 (0.0)
Pi-Sunyer et al, 2015 (13)						
Liraglutide, 3.0 mg	56	1992/2481 (80.3)	NR	238/2481 (9.6)	154/2481 (6.2)	1/2481 (0.04)
Placebo	56	786/1242 (63.3)	NR	45/1242 (3.6)	62/1242 (5.0)	2/1242 (0.2)
Wadden et al, 2020 (14)						
Liraglutide, 3.0 mg	56	136/142 (95.8)	101/142 (71.1)	12/142 (8.5)	6/142 (4.2)	0/142 (0.0)
Placebo	56	124/140 (88.6)	68/140 (48.6)	6/140 (4.3)	2/140 (1.4)	0/140 (0.0)
Rubino et al, 2022 (20)†						
Liraglutide, 3.0 mg	68	122/127 (96.1)	105/127 (82.7)	16/85 (12.6)	13/127 (10.2)	0/127 (0.0)
Placebo	68	81/85 (95.3)	47/85 (55.3)	3/85 (3.5)	6/85 (7.1)	0/85 (0.0)
Semaglutide						
Friedrichsen et al, 2021 (15)						
Semaglutide, 2.4 mg	20	29/36 (80.6)	NR	0/36 (0.0)	1/36 (2.8)	0/36 (0.0)
Placebo	20	33/36 (91.7)	NR	1/36 (2.8)	1/36 (2.8)	0.36 (0.0)
Gabe et al, 2024 (16)						
Semaglutide, 50 mg	20	25/30 (83.3)	17/30 (56.7)	2/30 (6.7)	0/30 (0.0)	0/30 (0.0)
Placebo	20	20/31 (64.5)	10/31 (32.3)	0/31 (0.0)	0/31 (0.0)	0/31 (0.0)
O'Neil et al, 2018 (17)†						
Semaglutide, 0.05–0.4 mg	52	668/718 (93.0)	526/718 (73.2)	64/718 (8.9)	58/718 (8.1)	1/718 (0.1)
Placebo	52	107/136 (78.7)	52/136 (38.2)	4/136 (2.9)	11/136 (8.1)	0/136 (0.0)
McGowan et al, 2024 (18)						
Semaglutide, 2.4 mg	52	NR	NR	NR	12/138 (8.7)	2/138 (1.5)
Placebo	52	NR	NR	NR	6/69 (8.7)	0/69 (0.0)
Knop et al, 2023 (19)						
Semaglutide, 50 mg	68	307/334 (91.9)	268/334 (80.2)	19/334 (5.7)	32/334 (9.6)	0/334 (0.0)
Placebo	68	285/333 (85.6)	154/333 (46.2)	12/333 (3.6)	29/333 (8.7)	0/333 (0.0)
Rubino et al, 2022 (20)†						
Semaglutide, 2.4 mg	68	120/126 (95.2)	106/126 (84.1)	4/126 (3.2)	10/126 (7.9)	0/126 (0.0)
Placebo	68	81/85 (95.3)	47/85 (55.3)	3/85 (3.5)	6/85 (7.1)	0/85 (0.0)
Wadden et al, 2021 (21)						
Semaglutide, 2.4 mg	68	390/407 (95.8)	337/407 (82.8)	24/407 (5.9)	37/407 (9.1)	0/407 (0.0)
Placebo	68	196/204 (96.1)	129/204 (63.2)	6/204 (2.9)	6/204 (2.9)	0/204 (0.0)
Wilding et al, 2021 (22)						
Semaglutide, 2.4 mg	68	1171/1306 (89.7)	969/1306 (74.2)	92/1306 (7.0)	128/1306 (9.8)	1/1306 (0.1)
Placebo	68	566/655 (86.4)	314/655 (47.9)	20/655 (3.1)	42/655 (6.4)	1/655 (0.2)
Garvey et al, 2022 (23)						
Semaglutide, 2.4 mg	104	146/152 (96.1)	125/152 (82.2)	9/152 (5.9)	12/152 (7.9)	1/152 (0.7)
Placebo	104	136/152 (89.5)	82/152 (53.9)	7/152 (4.6)	18/152 (11.8)	0/152 (0.0)
Tirzepatide						
Jastreboff et al, 2022 (24)						
Tirzepatide, 5–15 mg	72	1527/1896 (80.5)	NR	111/1896 (5.9)	116/1896 (6.2)	7/1896 (0.4)
Placebo	72	463/643 (72.0)	NR	17/643 (2.6)	44/643 (6.8)	4/643 (0.6)

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Table 4–Continued

Trial	Treatment Duration, *wk*	Any AE, *n/N (%)*	Gastrointestinal AE, *n/N (%)*	AE Leading to Treatment Discontinuation, *n/N (%)*	Serious AE, *n/N (%)*	Death, *n/N (%)*
Beinaglutide						
Chen et al, 2024 (25)						
Beinaglutide, 0.2 mg	16	240/286 (83.9)	170/286 (59.4)	17/286 (5.9)	2/286 (0.7)	0/286 (0.0)
Placebo	16	112/141 (79.4)	29/141 (20.5)	1/141 (0.7)	4/141 (2.8)	0/141 (0.0)
Efpeglenatide						
Pratley et al, 2019 (26)						
Efpeglenatide, 4–8 mg	20	207/235 (88.1)	174/235 (74.0)	31/235 (13.2)	6/235 (2.6)	0/235 (0.0)
Placebo	20	48/60 (80.0)	28/60 (46.7)	4/60 (6.7)	0/60 (0.0)	0/60 (0.0)
Exenatide						
Basolo et al, 2018 (27)						
Exenatide, 10 mcg	24	NR	NR	NR	0/41 (0.0)	NR
Placebo	24	NR	NR	NR	0/39 (0.0)	NR
Rosenstock et al, 2010 (28)						
Exenatide, 10 mcg	24	NR	NR	9/73 (12.3)	0/73 (0.0)	0/73 (0.0)
Placebo	24	NR	NR	3/79 (3.8)	0/79 (0.0)	0/79 (0.0)
Noiiglutide						
Li et al, 2024 (29)						
Noiiglutide, 0.12–0.36 mg	24	161/192 (83.9)	NR	6/192 (3.1)	6/192 (3.1)	0/192 (0.0)
Placebo	24	52/62 (83.9)	NR	0/62 (0.0)	3/62 (4.8)	0/62 (0.0)
Orforglipron						
Wharton et al, 2023 (30)						
Orforglipron, 12–45 mg	36	196/222 (88.3)	NR	35/222 (15.8)	7/222 (3.2)	0/222 (0.0)
Placebo	36	38/50 (76.0)	NR	1/50 (2.0)	0/50 (0.0)	0/50 (0.0)
JNJ-64565111						
Alba et al, 2021 (31)†						
JNJ-64565111, 5.0–10 mg	26	273/295 (92.5)	246/295 (83.4)	77/295 (26.1)	9/295 (3.1)	0/295 (0.0)
Placebo	26	43/60 (71.7)	17/60 (28.3)	0/60 (0.0)	4/60 (6.7)	0/60 (0.0)
Mazdutide						
Ji et al, 2023 (32)						
Mazdutide, 3–6 mg	24	177/186 (95.2)	NR	1/186 (0.5)	9/186 (4.8)	0/186 (0.0)
Placebo	24	50/62 (80.6)	NR	0/62 (0.0)	0/62 (0.0)	0/62 (0.0)
Survodutide (BI 456906)						
Jungnik et al, 2023 (33)						
Survodutide, 2.4–4.8 mg	16	35/36 (97.2)	NR	6/36 (16.7)	0/36 (0.0)	0/36 (0.0)
Placebo	16	9/9 (100.0)	NR	0/9 (0.0)	0/9 (0.0)	0/9 (0.0)
le Roux et al, 2024 (34)						
Survodutide, 0.6–4.8 mg	46	281/309 (90.9)	232/309 (75.1)	76/309 (24.6)	13/309 (4.2)	0/309 (0.0)
Placebo	46	58/77 (75.3)	32/77 (41.6)	3/77 (3.9)	5/77 (6.5)	0/77 (0.0)
Retatrutide						
Jastreboff et al, 2023 (35)						
Retatrutide, 1–12 mg	48	228/267 (85.4)	NR	27/267 (10.1)	10/267 (3.7)	1/267 (0.4)
Placebo	48	49/70 (70.0)	NR	0/70 (0.0)	3/70 (4.3)	0/70 (0.0)

AE = adverse event; GLP-1 RA = glucagon-like peptide-1 receptor agonist; NR = not reported.
* Events are pooled across all active doses (if applicable) and are reported as the number of participants with an AE among the total number of participants (percentage).
† Study is reported twice because it included 2 active groups.

in 19 RCTs, and changes in SBP and DBP were reported in 19 and 18 RCTs, respectively.

Safety

Adverse events were commonly reported in most participants for both the active treatment and placebo groups (Table 4). The majority were GI disorders (most commonly nausea, diarrhea, constipation, and vomiting), which occurred more frequently in the active groups than the placebo groups. Across all RCTs, the majority of GI disorders were transient, related to dose escalation, and mild to moderate in severity. No serious GI disorders, such as bowel obstruction or gastroparesis, were reported. Most AEs did not require treatment discontinuation. In addition, most treatment discontinuations occurred during the dose-escalation phase before the maintenance dose was reached. Select SAEs of interest included severe GI events, biliary disorders (cholecystitis

and cholelithiasis), pancreatitis, and psychiatric disorders. These outcomes were inconsistently reported across RCTs but were rare (severe GI and biliary disorders, ≤3.5%; pancreatitis, <2%; psychiatric disorders, ≤15% [including less severe events, such as insomnia and mood alterations]) in those that did report them (**Supplement Table 5**, available at Annals.org). Trial-specific safety outcomes are reported by dose in **Supplement Table 6** (available at Annals.org). Overall, there were no clear dose-dependent relationships.

Eight of the 26 RCTs reported at least 1 death, with 22 deaths reported overall (0.14%). These deaths occurred in 2 participants randomly assigned to liraglutide, 5 assigned to semaglutide, 7 assigned to tirzepatide, 1 assigned to retatrutide, and 7 assigned to placebo. The causes of these deaths are summarized in **Supplement Table 7** (available at Annals.org). The deaths in the participants assigned to semaglutide and retatrutide were not deemed by investigators to be related to the trial product. The investigators in the trials of the participants assigned to liraglutide and tirzepatide did not provide additional information about the causes of deaths and their relation to the trial products.

DISCUSSION

Our systematic review was designed to assess the efficacy and safety of GLP-1 RAs and co-agonists for weight loss in otherwise healthy adults with overweight or obesity and without diabetes. We found that, of the 12 GLP-1 RAs or co-agonists identified by our search, the greatest mean body weight reduction was reported in RCTs of retatrutide, tirzepatide, and semaglutide. Of these 3 agents, tirzepatide and semaglutide are already approved for long-term weight management and are commercially available in weekly injectable preparations. The premarket agents identified by our search also showed promising weight loss and cardioprotective effects. The use of all GLP-1 RAs or co-agonists led to decreased BMI, waist circumference, SBP, and DBP. Similar safety profiles were observed across agents. The rate of GI AEs was higher in the GLP-1 RA groups than the placebo groups. However, these events were described as transient, related to dose escalation, and mild to moderate in severity. The rate of AEs requiring treatment discontinuation, SAEs, and death was low across all RCTs.

Our review included the dual agonists tirzepatide (24), JNJ-64565111 (31), mazdutide (32, 37), and survodutide (33, 38) and the triple agonist retatrutide (35). In general, with the exception of semaglutide, RCTs of these dual and triple agonists generally reported numerically greater mean weight losses than single GLP-1 agonists, with co-agonists targeting the GIP pathway in addition to GLP-1 (tirzepatide and retatrutide) appearing to be the most efficacious. However, these RCTs did not compare these agents directly; thus, caution should be used when drawing conclusions about the comparative efficacy of these agents as the populations, control groups, and contexts may not be directly comparable.

GLP-1 RAs promote weight loss by acting on the hypothalamus to reduce appetite and increase satiety while also slowing gastric emptying and enhancing insulin regulation (39, 40). These combined central and peripheral effects help control food intake. GIP RAs modulate both insulin secretion and lipid metabolism (39, 41). When combined with GLP-1 RAs, they may complement appetite suppression and glucose control, leading to more effective weight loss through a synergistic effect on multiple metabolic pathways (42). GCG RAs aid in weight loss by stimulating fat breakdown (lipolysis), increasing energy expenditure, and boosting thermogenesis, which all contribute to a negative energy balance and reduced fat stores (43–45).

Previous systematic reviews and meta-analyses of RCTs have examined the efficacy and safety of GLP-1 RAs for weight loss in people with overweight or obesity, both with diabetes (46–48) and without diabetes (1, 49–51). However, these studies included patients with co-existing conditions, such as metabolic disorders or cardiovascular disease. Our systematic review differs from these previous studies in that we restricted inclusion to otherwise healthy adults with overweight or obesity, a demographic of potential interest to the general public.

Our review has several potential limitations. First, because this area is a rapidly expanding field of research, there is a lack of head-to-head RCTs, and most agents are included in only 1 or 2 RCTs. Second, due to differences in treatment periods between included RCTs and agents, we were unable to pool changes in continuous weight loss and cardiovascular risk factor outcomes across RCTs. Third, although our search had no language restrictions, RCTs published in languages other than English may not have been captured by the databases that were searched. Finally, lifestyle interventions (prescription of diet or exercise) varied across RCTs, which may have influenced our weight loss outcomes of interest.

Obesity is now recognized as a chronic disease that is associated with increased morbidity and mortality if it is not addressed and that requires lifelong treatment. This shift in perspective has led to a reevaluation of treatment approaches, including increasing use of effective pharmacotherapy. GLP-1 RAs have emerged as promising agents in this context due to their multifaceted effects on appetite regulation, energy homeostasis, and weight loss (52). Historically, weight loss medications such as phentermine and orlistat have had modest efficacy and substantial safety concerns (53, 54), leading to their limited use in clinical practice. GLP-1 RAs represent a newer class of medications that offer improved weight loss outcomes and appear to have a more favorable safety profile than older agents.

An important concern about the use of GLP-1 RAs for treatment of obesity is potential weight regain upon discontinuation of treatment. In an extension of the STEP 1 trial, participants initially randomly assigned to semaglutide regained 67% of their lost weight after 1 year off treatment, compared with 95% for those randomly assigned to placebo (55). Most cardiometabolic improvements also reverted to baseline levels after 1 year (55). Similarly, in the SURMOUNT-4 trial, participants who achieved a mean relative weight reduction of 20.9% after 36 weeks of treatment with tirzepatide regained 14% of baseline body weight when switched to placebo, whereas those who continued use of tirzepatide lost an extra 5.5% (56). These results suggest that ongoing treatment with GLP-1 RAs is necessary to sustain weight loss and health improvements. However, this phenomenon is not unique to GLP-1 RAs; it has been observed across various classes of medications used to treat chronic diseases, such as those for hypertension or diabetes (57), as well as in other treatments for obesity, including lifestyle interventions and other pharmacotherapies.

Trials assessing GLP-1 RAs indicate that most weight loss occurs early in treatment, with significant weight loss plateauing afterward. In our systematic review, RCTs with longer treatment durations demonstrate similar weight loss results to those with shorter follow-up, reinforcing the idea that continuous treatment may be required. This raises concerns about long-term adherence, as patients must weigh the risks for AEs associated with prolonged use against the substantial rebound effect upon treatment discontinuation. However, although common GI AEs, such as nausea and diarrhea, tend to be more pronounced during the initial phase, they often diminish with continued use, leading to improved tolerability. In addition, limited evidence on long-term safety is available. Although some concerns have been raised about GLP-1 RAs being associated with rare but severe SAEs, such as thyroid cancer (58, 59), current RCTs do not have the size or follow-up duration to assess these outcomes.

A potential inadvertent consequence of substantial weight loss is sarcopenia (reduction in skeletal muscle mass) (60, 61). However, prior studies have shown that the majority of GLP-1–induced weight loss comes from the loss of fat mass rather than lean body mass (62). The loss of 20% to 50% of lean body mass seen in these studies is consistent with weight loss induced by diet and bariatric surgery (63–67).

Beyond weight loss, GLP-1 RAs have also shown important cardiorenal protective effects. A review of 12 meta-analyses and 2 narrative reviews found that, among patients with diabetes, GLP-1 RAs were associated with a 12% to 14% risk reduction in a 3-point major adverse cardiovascular event outcome compared with placebo (68). In the SELECT trial, semaglutide reduced the incidence of death, nonfatal myocardial infarction, and nonfatal stroke among patients with established cardiovascular disease (69). In the STEP-HFpEF and STEP-HFpEF DM trials, randomization to semaglutide led to reduced symptoms and physical limitations and improved exercise function in patients with heart failure with preserved ejection fraction, both with and without diabetes (70, 71). In addition, subgroup analyses of several cardiovascular outcome trials have also demonstrated that GLP-1 RAs may help mitigate kidney-related outcomes, such as albuminuria, a decrease in estimated glomerular filtration rate, and risk for end-stage kidney disease in patients with and without diabetes (72, 73). The FLOW trial found that semaglutide slowed progression of kidney disease and reduced risk for kidney-related complications, including the need for renal replacement therapy, among patients with diabetes and chronic kidney disease (74). Emerging evidence suggests that GLP-1 RAs may also be beneficial in the management of several other conditions, including metabolic dysfunction–associated steatotic liver disease (75, 76), obstructive sleep apnea (77), polycystic ovary syndrome (78), and neurodegenerative diseases (79).

Oral formulations of GLP-1 RAs are being explored as an alternative to subcutaneous injections, potentially improving patient adherence and convenience. Trials of oral semaglutide and oral orforglipron both showed weight loss similar to that with injectable GLP-1 RAs (about 12%) (19, 30). Recently released data from a phase 2b RCT (NCT04707313) of oral danuglipron, a new agent, showed body weight reductions of up to −11.7% compared with weight gain of 1.7% with placebo at 32 weeks (80).

The dual co-agonist cagrilintide–semaglutide, a fixed-dose combination therapy of 2.4 mg of cagrilintide and 2.4 mg of semaglutide, is now also being investigated for weight loss in patients with obesity (81). Cagrilintide is a long-acting amylin analogue that potentiates semaglutide's weight loss effects. A phase 2 RCT in patients with diabetes showed a body weight reduction of −15.6% compared with −5.1% with semaglutide and −7.5% with cagrilintide alone (81). These encouraging results underscore the potential benefits of combination therapies, which may offer additive or synergistic effects on weight loss outcomes.

This review highlights the potential clinical benefits of GLP-1 RAs and co-agonists as tools in the management of obesity. Their demonstrated efficacy in promoting weight loss and improving cardiometabolic health underscores their potential role in addressing obesity as a chronic disease. As these agents become integrated into treatment regimens, it is essential for health care providers to monitor patients closely, particularly for potential adverse effects. The emergence of oral formulations and combination therapies may also enhance patient adherence and expand treatment options, highlighting the need for continued research to optimize the use of GLP-1 RAs and co-agonists across diverse populations.

Our systematic review found that in otherwise healthy adults with overweight or obesity and without

diabetes, RCTs reported the highest mean reductions in relative and absolute body weight with once-weekly retatrutide (which is not yet commercially available) followed by once-weekly tirzepatide and once-weekly semaglutide when compared with placebo. However, these trials did not compare therapies head-to-head, precluding conclusions about their comparative efficacy. All agents also showed modest benefits for blood pressure. The AEs related to GLP-1 RA use were mainly GI-related, transient, and mild to moderate in severity. Our results support the use of GLP-1 RAs and co-agonists for the treatment of overweight or obesity among patients without diabetes.

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Reproducible Research Statement: *Study protocol:* The search strategy, inclusion criteria, and data extraction methods are described in the Methods section of the text, with detailed search terms and databases used provided in the **Supplement.** The study protocol was developed in accordance with PRISMA guidelines and registered with PROSPERO (CRD42024505558). *Statistical code:* Code for generating descriptive summaries or visualizations can be shared on reasonable request (e-mail, mark.eisenberg@mcgill.ca). *Data set:* Because this systematic review relied on data from published trials, no primary data sets were generated.

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