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Quality and sustainability of weight loss with injectable incretin therapies in adults with obesity: an umbrella review of systematic reviews and meta analyses

Qualidade e sustentabilidade da perda de peso com terapias incretínicas injetáveis em adultos com obesidade: revisão guarda chuva de revisões sistemáticas e metanálises

Calidad y sostenibilidad de la pérdida de peso con terapias incretínicas inyectables en adultos con obesidad: revisión paraguas de revisiones sistemáticas y metaanálisis

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ABSTRACT

Objective: To synthesize evidence from systematic reviews on the magnitude and sustainability of weight loss with injectable incretin therapies in adults with obesity, including weight regain after discontinuation, body composition, quality of life, and safety. Methodology: An umbrella review was conducted according to PRIOR, PRISMA 2020, and Joanna Briggs Institute guidance. PubMed, the Cochrane Library, Epistemonikos, and Google Scholar were searched through July 23, 2026. Systematic reviews with or without meta analysis addressing liraglutide, semaglutide, tirzepatide, retatrutide, or related incretin agonists were eligible. Methodological quality was appraised with AMSTAR 2. Because primary trials overlapped substantially, estimates were not statistically recombined. Results: Eighteen reviews were included. Representative estimates showed mean placebo corrected weight reductions of 4.72% with liraglutide, 10.73% with semaglutide, and 16.03% with tirzepatide; retatrutide reached 22.1% in a still limited evidence base. Discontinuation was followed by clinically relevant regain, commonly exceeding 5 kg, with faster regain after larger initial losses. About one quarter of total weight reduction reflected lean mass in body composition analyses. Gastrointestinal events increased treatment withdrawal, whereas serious events remained uncommon. Conclusion: Injectable incretin therapies produce substantial weight loss, but the quality and durability of benefit depend on continued treatment, muscle preservation, tolerability, and explicit maintenance planning.

Keywords: Obesity. Glucagon-like peptide-1 receptor agonists. Weight loss. Body composition. Umbrella review.

RESUMO

Objetivo: Sintetizar a evidência proveniente de revisões sistemáticas sobre magnitude e sustentabilidade da perda de peso com terapias incretínicas injetáveis em adultos com obesidade, considerando reganho após interrupção, composição corporal, qualidade de vida e segurança. Metodologia: Revisão guarda chuva conduzida de acordo com PRIOR, PRISMA 2020 e orientações do Joanna Briggs Institute. PubMed, Cochrane Library, Epistemonikos e Google Scholar foram pesquisados até 23 de julho de 2026. Revisões sistemáticas com ou sem metanálise sobre liraglutida, semaglutida, tirzepatida, retatrutida ou agonistas incretínicos relacionados foram elegíveis. A qualidade metodológica foi avaliada pelo AMSTAR 2. Devido à sobreposição dos ensaios primários, não foi realizada nova combinação estatística. Resultados: Dezoito revisões foram incluídas. Estimativas representativas indicaram reduções médias de peso em relação ao placebo de 4,72% com liraglutida, 10,73% com semaglutida e 16,03% com tirzepatida; a retatrutida atingiu 22,1% em evidência ainda limitada. A interrupção foi seguida por reganho relevante, frequentemente superior a 5 kg, com recuperação mais rápida após perdas iniciais maiores. Aproximadamente um quarto da redução ponderal correspondeu à massa magra em análises de composição corporal. Eventos gastrointestinais aumentaram a descontinuação, enquanto eventos graves permaneceram incomuns. Conclusão: As terapias incretínicas proporcionam perda de peso substancial, porém a qualidade e a durabilidade do benefício dependem de tratamento continuado, preservação muscular, tolerabilidade e planejamento da manutenção.

Palavras-chave: Obesidade. Agonistas do receptor do peptídeo-1 semelhante ao glucagon. Perda de peso. Composição corporal. Revisão guarda-chuva.

RESUMEN

Objetivo: Sintetizar la evidencia de revisiones sistemáticas sobre la magnitud y sostenibilidad de la pérdida de peso con terapias incretínicas inyectables en adultos con obesidad, incluido el aumento de peso tras la suspensión, la composición corporal, la calidad de vida y la seguridad. Metodología: Se realizó una revisión paraguas conforme a PRIOR, PRISMA 2020 y las orientaciones del Joanna Briggs Institute. Se consultaron PubMed, Cochrane Library, Epistemonikos y Google Scholar hasta el 23 de julio de 2026. Se incluyeron revisiones sistemáticas con o sin metaanálisis sobre liraglutida, semaglutida, tirzepatida, retatrutida u otros agonistas incretínicos relacionados. La calidad metodológica se evaluó mediante AMSTAR 2. Debido a la superposición de ensayos primarios, no se efectuó una nueva combinación estadística. Resultados: Se incluyeron 18 revisiones. Las estimaciones representativas mostraron reducciones medias de peso corregidas por placebo de 4,72% con liraglutida, 10,73% con semaglutida y 16,03% con tirzepatida; la retatrutida alcanzó 22,1% con evidencia aún limitada. La suspensión fue seguida por una recuperación clínicamente relevante, frecuentemente superior a 5 kg. Cerca de una cuarta parte de la pérdida total correspondió a masa magra. Los eventos gastrointestinales aumentaron la retirada, mientras que los eventos graves fueron poco frecuentes. Conclusión: Estas terapias producen pérdidas sustanciales, pero la calidad y duración del beneficio dependen de la continuidad terapéutica, la preservación muscular, la tolerabilidad y la planificación del mantenimiento.

Palabras clave: Obesidad. Agonistas del receptor del péptido-1 similar al glucagón. Pérdida de peso. Composición corporal. Revisión paraguas.

1. INTRODUCTION

Obesity is a chronic, relapsing, and heterogeneous disease whose clinical consequences extend beyond body weight. Excess adiposity contributes to type 2 diabetes, cardiovascular disease, sleep disordered breathing, osteoarthritis, fatty liver disease, several cancers, impaired mobility, and reduced quality of life. These consequences arise from a combination of adipose tissue dysfunction, ectopic fat

deposition, mechanical burden, inflammation, and social disadvantage. Accordingly, treatment decisions should not be reduced to the number of kilograms lost. A clinically complete evaluation must consider the durability of weight reduction, preservation of functional tissue, changes in symptoms and daily life, treatment burden, and the likelihood that benefits will persist after medication is stopped (World Health Organization, 2025).

Injectable incretin based therapies have changed the expected magnitude of nonsurgical weight reduction. Liraglutide introduced a daily glucagon like peptide 1 receptor agonist for chronic weight management. Once weekly semaglutide produced larger mean reductions, and the combined glucose dependent insulinotropic polypeptide and GLP 1 receptor agonist tirzepatide extended these results further. Triple receptor agonists, particularly retatrutide, have generated additional interest because early trials reported reductions approaching those observed after some metabolic operations. This therapeutic evolution has been accompanied by rapid growth in randomized trials, comparative network meta analyses, drug specific Cochrane reviews, body composition reviews, and reviews focused on withdrawal or adverse events (Damen et al., 2026; Moiz et al., 2025; Nong et al., 2026).

The expression weight loss injections has become common in public discussion, but it can obscure important clinical distinctions. These medicines differ in receptor targets, dosing schedules, evidence maturity, regulatory status, tolerability, and the populations in which they were studied. More importantly, a large numerical reduction in body weight does not automatically represent high quality weight loss. Loss of adipose tissue is desirable, whereas excessive reduction in skeletal muscle may impair strength, resting energy expenditure, and resilience, particularly in older adults or people with limited protein intake and physical activity. Recent body composition syntheses suggest that a meaningful fraction of the weight lost with incretin therapy may consist of lean tissue, although the proportion varies according to method, population, and agent (Bikou et al., 2024; Karakasis et al., 2025; Rochira et al., 2024).

Durability is another unresolved dimension. Obesity pharmacotherapy is often initiated with expectations formed by short or medium term trial results, yet treatment is interrupted in practice because of adverse effects, cost, supply limitations, pregnancy planning, preference, or achievement of a target weight. Withdrawal extensions and recent meta analyses consistently indicate weight regain after treatment cessation. The absolute amount recovered tends to be larger after more potent therapy because the initial loss is larger, and several cardiometabolic improvements also move back toward baseline. This pattern challenges the view of incretin therapy as a temporary course and instead supports the chronic disease model of continued management (Berg et al., 2025; Budini et al., 2026; Tzang et al., 2025; West et al., 2026).

Patient experience is equally relevant. Gastrointestinal symptoms can be transient and manageable for some individuals, but they can lead to dose reduction or withdrawal in others. Changes in satiety, food preoccupation, emotional eating, physical function, and weight related quality of life may be highly valued even when generic quality of life instruments show small mean effects. Conversely, anxiety about access, fear of regain, injection burden, and uncertainty about indefinite treatment can diminish acceptability. Integrating quantitative efficacy with body composition, withdrawal, patient reported outcomes, and safety therefore provides a more useful account than ranking agents by weight change alone (Ibsen et al., 2025; Ismaiel et al., 2025; Pierret et al., 2025).

The expanding number of systematic reviews creates a second problem: the same pivotal trials are repeatedly included in multiple syntheses. Reading each meta analysis independently may give an exaggerated impression of evidence volume because the apparent replication often reflects recycled primary data. An umbrella review can map this overlap, prioritize the most recent and methodologically rigorous sources, and identify conclusions that remain stable across different review teams. It can also expose outcomes for which enthusiasm is ahead of evidence, such as long term lean mass preservation, strategies for safe discontinuation, and the performance of emerging triple agonists.

This umbrella review aimed to synthesize systematic review evidence on the magnitude, quality, and sustainability of weight loss achieved with injectable incretin based therapies in adults with overweight or obesity. The specific objectives were to compare representative weight outcomes across agents, characterize regain after discontinuation, evaluate changes in fat and lean mass, summarize patient reported outcomes, and examine tolerability and serious adverse events.

2. METHODOLOGY

This study was designed as an umbrella review of systematic reviews. Reporting followed the Preferred Reporting Items for Overviews of Reviews statement and relevant items from PRISMA 2020. Methodological decisions were informed by the Joanna Briggs Institute guidance for umbrella reviews (Aromataris et al., 2024; Gates et al., 2022; Page et al., 2021). A structured protocol was prepared before extraction. The protocol was not prospectively registered, which is acknowledged as a limitation.

The review question was organized according to population, intervention, comparator, outcomes, and study design. The population comprised adults aged 18 years or older with overweight or obesity, whether or not type 2 diabetes or another cardiometabolic condition was present. Eligible interventions were injectable incretin based medicines used for weight management, including liraglutide, semaglutide, tirzepatide, retatrutide, and related GLP 1 receptor, GIP/GLP 1 receptor, or multiple receptor agonists.

Comparators included placebo, lifestyle intervention, another active medicine, treatment continuation, or treatment withdrawal.

The outcomes were organized into five domains. The efficacy domain included absolute and percentage weight change, body mass index, waist circumference, and achievement of clinically relevant thresholds. The durability domain included maintenance during treatment, weight regain after discontinuation, and reversal of cardiometabolic effects. The body composition domain included fat mass, visceral adipose tissue, lean mass, skeletal muscle, and bone outcomes. The patient reported domain included physical and mental quality of life, eating behavior, treatment experience, and functional wellbeing. The safety domain included gastrointestinal symptoms, gallbladder events, pancreatitis, serious adverse events, and withdrawal because of adverse events.

Systematic reviews with or without meta analysis were eligible when they described a reproducible search, explicit eligibility criteria, and a structured synthesis of primary studies. Reviews could include randomized trials, nonrandomized comparative studies, or qualitative studies when the focus was patient experience. Pediatric only reviews, narrative reviews, commentaries, protocols, reviews restricted to a disease population without separable overweight or obesity findings, and reviews of oral incretin therapy alone were excluded. When two publications represented updates from the same review group and addressed the same question, the most complete or recent version was retained.

Searches were conducted in PubMed, the Cochrane Library, Epistemonikos, and Google Scholar from database inception through July 23, 2026. Search terms combined controlled vocabulary and free text for obesity, overweight, GLP 1 receptor agonists, incretin therapy, liraglutide, semaglutide, tirzepatide, retatrutide, systematic review, and meta analysis. Reference lists of included reviews and recent clinical guidelines were examined, and forward citation searches were used to identify 2025 and 2026 publications. No language restriction was applied during searching, but an English, Portuguese, or Spanish full text was required for detailed appraisal. The complete search logic is presented in Appendix A.

Titles and abstracts were screened against the eligibility criteria, followed by full text assessment. One reviewer completed screening and extraction, and every included citation and central numerical estimate was checked against the source report or an authoritative bibliographic record. This verification procedure reduced transcription error but did not replace independent duplicate review. Data were entered into a standardized matrix containing search date, number and design of primary studies, population, interventions, duration, outcomes, pooled estimates, certainty assessments, funding information, and limitations.

Methodological quality was appraised with AMSTAR 2, which evaluates critical domains such as protocol development, adequacy of the search, justification of exclusions, risk of bias assessment, appropriateness of synthesis, consideration of risk of bias in interpretation, and investigation of publication bias (Shea et al., 2017). Global confidence was classified as high, moderate, low, or critically low. The classification was not produced by adding domain scores. Cochrane reviews and living network meta analyses were generally prioritized when their scope matched the review question because they used recent searches, explicit risk of bias methods, and formal certainty assessment.

Primary trial overlap was expected to be substantial, particularly for the STEP, SCALE, SURMOUNT, and phase 2 retatrutide programs. Therefore, this umbrella review did not pool pooled estimates. For each domain, a representative estimate was selected from the most recent high confidence review with the closest population and dose. Other reviews were used to test consistency, expand outcomes, and describe uncertainty. This overlap aware approach avoids treating the same trial participants as independent observations. Numerical results are reported with 95% confidence intervals when provided by the source review.

Because the included material consisted exclusively of published studies and contained no identifiable participant data, research ethics committee approval was not required. All extracted data used in the synthesis are presented in the tables or are traceable to the cited reviews.

Table 1 summarizes the eligibility framework applied during screening and extraction.

Table 1. Eligibility criteria for the umbrella review

Domain	Included	Excluded
Population	Adults with overweight or obesity, with or without cardiometabolic comorbidity	Pediatric only populations or disease specific samples without separable obesity data
Intervention	Injectable liraglutide, semaglutide, tirzepatide, retatrutide, or related incretin agonists	Oral agents alone, nonincretin medicines alone, or surgery without a separable pharmacotherapy arm
Comparator	Placebo, lifestyle care, another active drug, continued treatment, or withdrawal	No restriction when the review addressed body composition, patient experience, or adverse events
Outcomes	Weight change, regain, body composition, quality of life, eating behavior, tolerability, serious adverse events	Reviews reporting no outcome relevant to obesity treatment
Study design	Systematic review with or without meta analysis; qualitative systematic review for patient experience	Narrative review, commentary, protocol, primary study, or conference abstract without a complete review report
Publication	Full report available by July 23, 2026	Superseded duplicate or unavailable full report

Source: Authors, 2026.

The framework allowed broad clinical inclusion while requiring that obesity related findings could be separated from disease specific evidence. It also preserved qualitative evidence on treatment experience, which would have been lost under a meta analysis only criterion.

3. RESULTS AND DISCUSSIONS

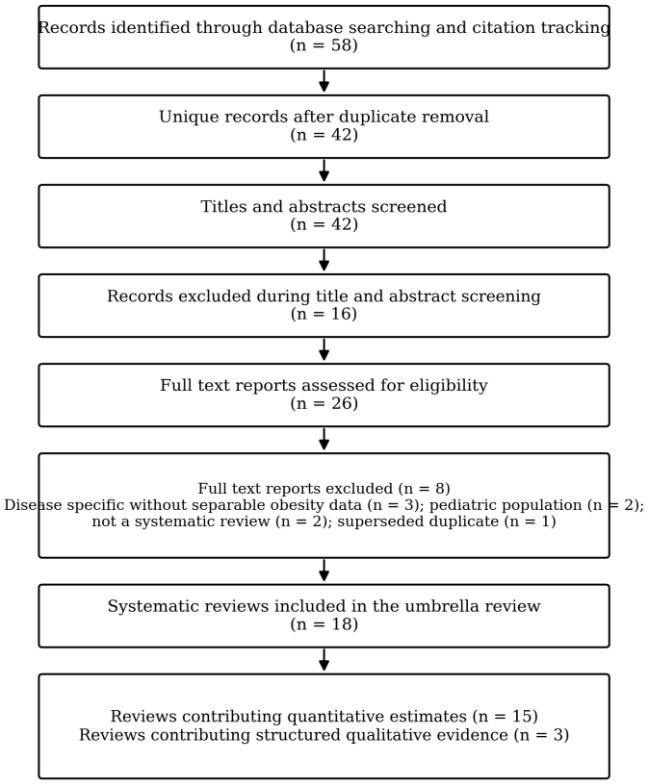
3.1 Results

3.1.1 Study selection and review characteristics

The searches and citation tracking identified 58 records. After duplicate removal, 42 unique records were screened and 26 full text reports were assessed. Eighteen reviews met the eligibility criteria. Fifteen included a quantitative synthesis and three contributed structured qualitative or descriptive evidence. Full text exclusions most often reflected disease specific scope without separable obesity data, pediatric populations, or absence of systematic methods.

Figure 1 presents the selection process. It should be read as a map of the umbrella review search rather than as a count of primary clinical trials. The 18 included reviews repeatedly drew on several of the same pivotal trials, which is why the number of reviews cannot be interpreted as 18 independent bodies of participant data.

Figure 1. Flow of systematic review identification and selection



Source: Authors, 2026, based on PRIOR and PRISMA 2020.

The figure shows that fewer than half of the screened unique records entered the final synthesis. The largest reduction occurred during title and abstract screening, while full text exclusions were mainly related to population and review design.

The included reviews were published between 2024 and 2026, with one older methodological context source retained only in the references. Their scopes ranged from drug specific Cochrane reviews to broad network meta analyses, discontinuation syntheses, body composition studies, patient experience reviews, and safety analyses. Review sizes varied from six primary studies to more than 260 trials. Participant numbers ranged from approximately 2,200 in body composition analyses to more than 100,000 in broad safety and mental health syntheses. Tables 2 and 3 describe the clinical and outcome specific reviews.

Table 2. Reviews addressing efficacy, comparative effectiveness, and treatment discontinuation

Review	Scope and data	Population	Main contribution	AMSTAR 2
Bracchiglione et al. (2025)	Semaglutide; 18 randomized trials; 27,949 participants	Adults with obesity, with and without diabetes	Mean placebo corrected weight reduction of 10.73% in medium term follow up; withdrawal because of adverse events increased	High
Franco et al. (2025)	Tirzepatide; 9 randomized trials; 7,111 participants	Adults with obesity, with and without diabetes	Mean placebo corrected weight reduction of 16.03%; large increase in achieving at least 5% loss	High
Meza et al. (2025)	Liraglutide; 24 randomized trials; 9,937 participants	Adults with obesity, with and without diabetes	Mean placebo corrected weight reduction of 4.72%; certainty lower than for newer agents	High
Moiz et al. (2025)	GLP 1 agonists and coagonists; randomized trials	Adults without diabetes	Tirzepatide and semaglutide produced the largest established reductions; retatrutide was promising but less mature	High
Damen et al. (2026)	Living network meta analysis; 69 studies; 112,511 participants	Adults with overweight or obesity	Semaglutide and tirzepatide showed the most favorable established weight outcomes across patient important endpoints	High
Nong et al. (2026)	Network meta analysis; 262 trials; nearly 100,000 participants	Adults with overweight or obesity	Large comparative evidence base; incretin therapies led efficacy rankings, with certainty varying by drug and outcome	High
Berg et al. (2025)	Discontinuation review; 8 randomized trials; 2,372 participants	Adults stopping GLP 1 therapy	Pooled regain was about 2.20 kg after liraglutide and 9.69 kg after semaglutide or tirzepatide	Moderate
Tzang et al. (2025)	Discontinuation review; 18 randomized trials; 3,771 participants	Adults after GLP 1 agonist withdrawal	Obesity subgroup regained 5.63 kg; longer follow up showed greater regain and metabolic rebound	High
West et al. (2026)	Medication cessation review; 37 studies; more than 9,300 participants	Adults stopping weight management medicines	Average regain was approximately 0.4 kg per month, about four times the rate after behavioral programs	High
Budini et al. (2026)	Nonlinear meta regression of GLP 1 cessation studies	Adults after cessation	Regain was rapid early and then decelerated; most initial loss was projected to be recovered, although not always fully	Moderate
Kolli et al. (2025)	Meta analysis of antiobesity drug discontinuation	Adults after drug withdrawal	Confirmed clinically important regain across medicines, with heterogeneity by agent and follow up	Low

Source: Authors, 2026. AMSTAR 2 global confidence reflects appraisal in the present umbrella review.

The clinical reviews were consistent in identifying a gradient of average efficacy from liraglutide to semaglutide and tirzepatide. Discontinuation reviews were also directionally concordant, but the absolute amount regained depended strongly on initial response, agent, and duration of post withdrawal observation.

Table 3. Reviews addressing body composition, patient reported outcomes, and safety

Review	Scope	Outcome domain	Main contribution	AMSTAR 2
Karakasis et al. (2025)	Body composition network meta analysis; 22 randomized trials; 2,258 participants	Weight, fat mass, and lean mass	Mean lean mass reduction of 0.86 kg; lean tissue represented about one quarter of total weight reduction	Moderate
Bikou et al. (2024)	Semaglutide lean mass systematic review; 6 studies	Lean mass and proportional composition	Absolute lean mass often decreased, but the percentage of body weight represented by lean tissue was usually maintained or increased	Low
Rochira et al. (2024)	Tirzepatide body composition systematic review	Fat mass, visceral fat, and fat free mass	Consistent fat and visceral adipose reduction; insufficient evidence for firm conclusions about muscle preservation	Low
Pierret et al. (2025)	Mental health meta analysis; 80 randomized trials; 107,860 participants	Psychiatric events, eating behavior, and quality of life	No clear increase in psychiatric adverse events; small improvements in eating behavior and physical and mental quality of life	High
Ibsen et al. (2025)	Qualitative patient experience review	Adults using GLP 1 agonists	Patients often accepted gastrointestinal symptoms in exchange for benefit and described reduced cravings and improved daily function	Low
Ismaiel et al. (2025)	Gastrointestinal safety network meta analysis; 39 reports; 33,354 participants	Adults without diabetes with overweight or obesity	Nausea, vomiting, diarrhea, and constipation were the principal adverse events; patterns varied by agent and dose	Moderate
Misra et al. (2025)	Retatrutide systematic review of clinical trials	Adults with obesity	Very large early weight effects with gastrointestinal adverse events; limited number and duration of trials	Low

Source: Authors, 2026. AMSTAR 2 global confidence reflects appraisal in the present umbrella review.

These outcome specific reviews broadened the interpretation of efficacy. They showed that adipose tissue reduction is accompanied by some lean tissue loss, that patient perceived benefits may exceed changes measured by generic scales, and that gastrointestinal symptoms remain the most consistent barrier to continuation.

3.1.2 Magnitude of weight reduction

Three Cochrane reviews provided the most directly comparable drug specific estimates. For liraglutide, the mean difference in percentage body weight versus placebo was 4.72 percentage points (95% CI 4.12 to 5.32 in favor of liraglutide) across 16 studies with 6,050 participants, although certainty was judged very low because of heterogeneity and limitations in the underlying evidence. Semaglutide produced a mean placebo corrected reduction of 10.73 percentage points (95% CI 9.21 to 12.24) across 15 studies with 8,651 participants, with high certainty. Tirzepatide produced a mean reduction of 16.03 percentage

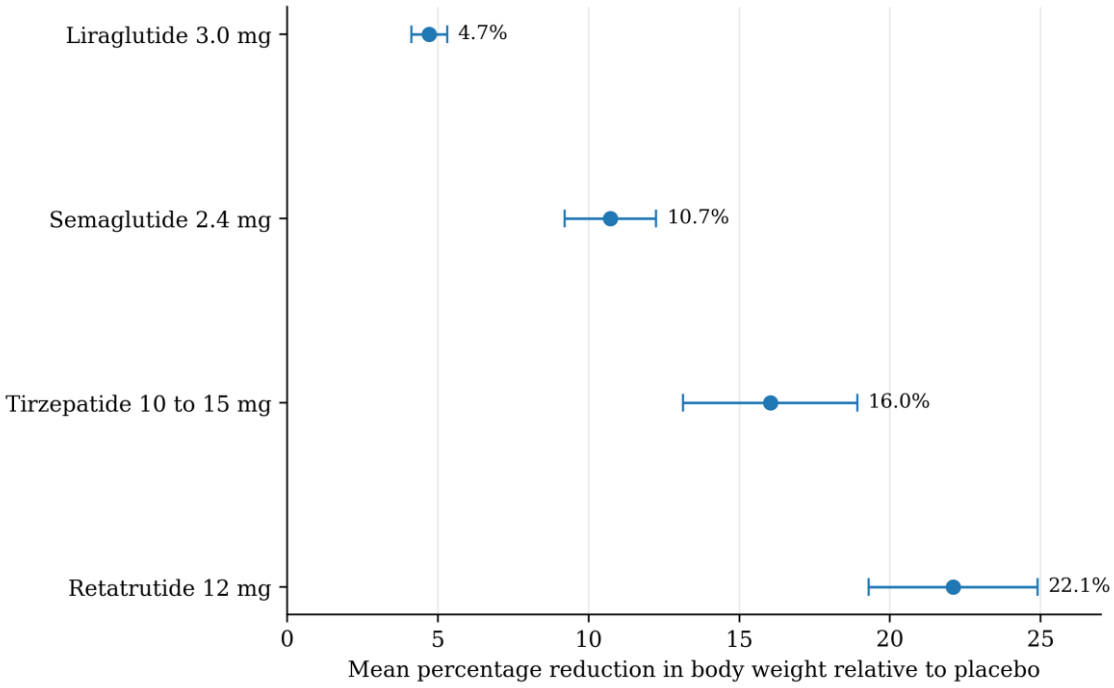
points (95% CI 13.14 to 18.91) across eight studies with 6,317 participants, with moderate certainty (Bracchiglione et al., 2025; Franco et al., 2025; Meza et al., 2025).

Threshold outcomes supported the same ordering. The relative probability of losing at least 5% of baseline weight was 2.10 with liraglutide, 2.68 with semaglutide, and 3.60 with tirzepatide compared with placebo. These relative effects should not be directly compared as if they arose from one trial because baseline risk, duration, dose, diabetes status, and cointerventions differed. Nevertheless, the agreement across drug specific and network reviews indicates that semaglutide and tirzepatide produce substantially greater mean weight reductions than liraglutide at approved obesity doses.

Emerging agents may extend the gradient. Moiz et al. (2025) reported estimated placebo corrected mean reductions of 5.8% for liraglutide 3.0 mg, 13.9% for semaglutide 2.4 mg, 17.8% for tirzepatide 15 mg, and up to 22.1% for retatrutide 12 mg. Retatrutide estimates were derived from a smaller and less mature trial program, so they should be interpreted as a signal rather than a settled comparative result. The 2026 living and network reviews also emphasized that evidence certainty depends on the number of trials, consistency, and duration, not merely on rank position (Damen et al., 2026; Nong et al., 2026).

Figure 2 displays representative placebo corrected estimates selected from the highest confidence reviews. The graphic is descriptive and does not constitute a new network comparison.

Figure 2. Representative percentage reductions in body weight with injectable incretin therapies



Source: Authors, 2026, using representative estimates from Meza et al. (2025), Bracchiglione et al. (2025), Franco et al. (2025), and Moiz et al. (2025).

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The reader should observe the increasing magnitude of average weight reduction across successive incretin mechanisms. The wider uncertainty and smaller evidence base for retatrutide mean that its apparent advantage is less secure than the established estimates for semaglutide and tirzepatide.

3.1.3 Sustainability and weight regain after discontinuation

All discontinuation syntheses identified weight regain after treatment cessation. Tzang et al. (2025) pooled 18 randomized trials with 3,771 participants and found a mean regain of 5.63 kg (95% CI 3.52 to 7.73) in obesity populations. Follow up longer than 26 weeks was associated with greater regain than shorter follow up, approximately 7.31 kg compared with 2.51 kg. Agent specific analyses suggested more absolute regain after semaglutide than after liraglutide, which is expected because semaglutide generally produces a larger initial loss.

Berg et al. (2025) similarly estimated regain of about 2.20 kg after liraglutide and 9.69 kg after semaglutide or tirzepatide. The pooled categories combined trials with different treatment durations and withdrawal designs, so the numerical difference does not prove that one medicine biologically causes faster rebound. It mainly demonstrates that greater pharmacologic efficacy creates more weight that can be recovered when the active appetite and energy balance effects are removed.

West et al. (2026) placed the problem in a broader treatment context. Across 37 studies and more than 9,300 participants, weight after medication cessation increased by approximately 0.4 kg per month, compared with approximately 0.1 kg per month after the end of behavioral programs. Their models projected return toward baseline weight in roughly 1.7 years and return of cardiometabolic markers toward baseline in approximately 1.4 years, although individual trajectories varied substantially.

The nonlinear analysis by Budini et al. (2026) suggested that regain is not constant. It is fastest during the early months and then decelerates, with a projected plateau below complete recovery in some analyses. This trajectory matters clinically because a short post withdrawal assessment can underestimate the eventual amount regained, whereas a constant linear model may overestimate late regain. Across reviews, evidence was insufficient to establish whether gradual tapering, switching agents, lower maintenance doses, resistance training, intensified dietary support, or other structured strategies reliably prevent regain.

Cardiometabolic rebound accompanied weight regain. In the Tzang synthesis, glycated hemoglobin rose after withdrawal, and waist circumference, body mass index, systolic blood pressure, and fasting glucose moved in an unfavorable direction. The available evidence therefore indicates that discontinuation

is not simply a cosmetic change in weight. It can reverse part of the metabolic improvement achieved during treatment.

3.1.4 Body composition and the quality of weight loss

The most comprehensive body composition network meta analysis included 22 randomized trials and 2,258 participants. Across GLP 1 receptor agonists and coagonists, total weight decreased by a mean of 3.55 kg, fat mass by 2.95 kg, and lean mass by 0.86 kg. The authors estimated that lean tissue accounted for approximately one quarter of total weight reduction. Tirzepatide 15 mg and semaglutide 2.4 mg were among the most effective options for total and fat mass reduction but were not the strongest for preserving absolute lean mass (Karakasis et al., 2025).

The clinical meaning of lean mass change requires caution. Lean mass measured by dual energy x ray absorptiometry includes water, organs, connective tissue, and muscle. A decrease in absolute lean mass is expected during major weight loss and does not necessarily indicate sarcopenia. The relevant questions are whether muscle loss is disproportionate, whether strength and physical performance decline, and whether high risk groups lose the reserve needed for mobility or recovery from illness. Few primary trials measured these functional outcomes.

The semaglutide review by Bikou et al. (2024) found variable absolute lean mass reductions across six studies, occasionally representing a large share of total weight loss. At the same time, the relative percentage of body weight composed of lean tissue was generally maintained or increased because fat mass fell more sharply. This apparent paradox illustrates why both absolute and proportional results should be reported. An increasing lean mass percentage does not mean muscle was gained.

The tirzepatide review by Rochira et al. (2024) consistently found reductions in total and visceral fat but judged evidence on fat free mass insufficient for firm conclusions. Retatrutide evidence was even less mature. Across reviews, older adults, people with baseline sarcopenia, individuals with severe dietary restriction, and patients with low physical activity were underrepresented. Evidence on bone mineral density and fracture was also sparse.

No included review established an optimal muscle preservation intervention during incretin therapy. Nevertheless, the pattern of evidence supports measuring more than weight in individuals at risk. Dietary protein adequacy, progressive resistance exercise, functional assessment, and avoidance of unnecessarily rapid undernutrition are biologically plausible components of care, but their effectiveness alongside modern incretin agents requires dedicated randomized trials.

3.1.5 Quality of life, eating behavior, and patient experience

Drug specific Cochrane reviews found small mean improvements in physical function or weight related quality of life, but several effects did not clearly reach thresholds for clinical importance. Semaglutide improved the physical function component of the Short Form 36 by 2.12 points, and tirzepatide improved the physical domain of the Impact of Weight on Quality of Life measure by 9.91 points in pooled analyses. Liraglutide had a less certain effect. Differences among instruments, reporting time points, and missing data limited cross drug comparison (Bracchiglione et al., 2025; Franco et al., 2025; Meza et al., 2025).

Pierret et al. (2025) synthesized 80 randomized trials with 107,860 participants. GLP 1 therapies were not associated with a clear increase in serious or nonserious psychiatric adverse events. Mean effects on depressive symptoms were close to null. Small favorable effects were observed for restrained eating, emotional eating, mental quality of life, physical quality of life, diabetes specific quality of life, and weight related quality of life. These effects suggest benefit but should not be overstated, as standardized mean differences were generally small.

Qualitative findings added context that was not captured by pooled scale scores. Patients described reduced hunger, fewer sweet cravings, less persistent thinking about food, improved movement, and greater participation in daily activities. Some were willing to tolerate nausea or altered bowel habits because the perceived weight and functional benefits were important. Others experienced treatment as burdensome, particularly when adverse symptoms affected meals, work, or social life. Device usability and expectations about long term treatment also influenced continuation (Ibsen et al., 2025).

Evidence on body image, stigma, treatment related anxiety, compulsive eating, and fear of regain remained fragmented. Most trials were designed for weight outcomes and did not prespecify detailed psychological measures. The absence of a pooled increase in psychiatric adverse events is reassuring, but it does not eliminate the need for individual assessment in people with active eating disorders, severe depression, suicidal thoughts, or complex psychotropic treatment.

3.1.6 Tolerability, treatment withdrawal, and serious adverse events

Gastrointestinal symptoms were the most consistent adverse effects across agents. The network meta analysis by Ismaiel et al. (2025), which included 39 reports and 33,354 adults without diabetes, identified nausea, vomiting, diarrhea, and constipation as the dominant events. Nausea increased with all evaluated GLP 1 therapies, while constipation was particularly evident with semaglutide and liraglutide. Dose escalation increased risk, although some dose response curves appeared to plateau.

The Cochrane reviews showed that adverse events translated into treatment withdrawal. Compared with placebo, the relative risk of withdrawal because of adverse events was 1.98 with liraglutide, 1.84 with semaglutide, and 2.06 with tirzepatide. Any or nonserious adverse events were also more common, but serious adverse events did not show a clear increase in the pooled trial evidence. The serious event estimates were imprecise for rare outcomes and should not be interpreted as proof of absence of risk.

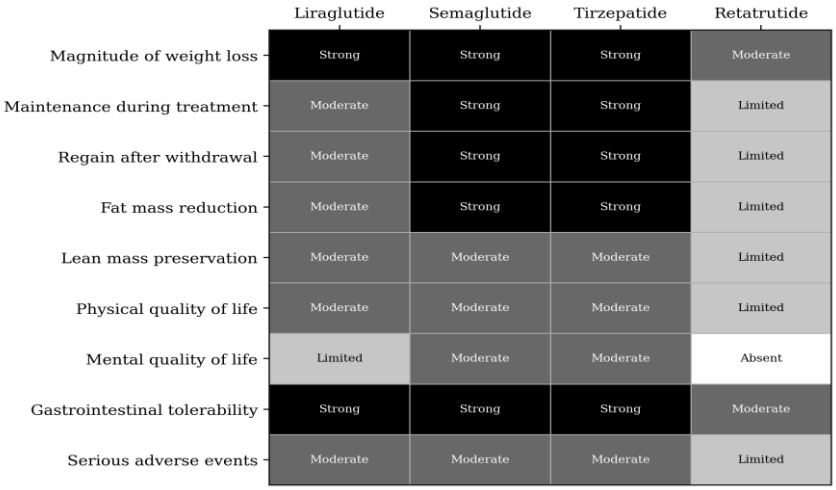
Pancreatitis and gallbladder events were uncommon and inconsistently reported. Ismaiel et al. (2025) found no clear pancreatitis signal, but the number of events was small. Reviews also noted that trials are not well suited to detect very rare or delayed outcomes. Randomized trial evidence should therefore be complemented by pharmacovigilance and high quality observational studies, particularly as exposure expands to younger people and long treatment durations.

Treatment continuation in routine care is influenced by more than biological tolerability. Cost, insurance decisions, supply shortages, injection preference, and access to follow up can interrupt therapy even when it is effective. These factors were not adequately represented in efficacy trials and were only partially captured in qualitative evidence. A medicine with high biological efficacy can have low real world effectiveness when sustained access is uncertain.

3.1.7 Integrated evidence map and methodological confidence

Figure 3 integrates the relative maturity of evidence across agents and outcome domains. The categories reflect the amount, consistency, and methodological confidence of review evidence rather than the magnitude of treatment effect.

Figure 3. Evidence maturity across therapies and clinically relevant domains



Source: Authors, 2026. Categories are qualitative and based on the number, consistency, and AMSTAR 2 confidence of included reviews.

The evidence map shows that weight efficacy and gastrointestinal tolerability are the best studied domains. Evidence becomes less complete for long term maintenance, lean mass preservation, mental quality of life, and emerging retatrutide therapy. Darker cells should not be read as a recommendation for a particular agent; they indicate greater evidentiary maturity.

Table 4. Integrated interpretation of benefits, limitations, and clinical implications

Domain	Consistent finding	Main uncertainty	Practical implication
Weight efficacy	Large and consistent reductions, strongest established evidence for semaglutide and tirzepatide	Indirect comparisons and repeated use of the same pivotal trials	Discuss expected mean loss and individual variability; avoid promising a fixed result
Durability	Benefits are maintained while therapy continues; regain is common after cessation	Few trials test maintenance strategies or gradual dose reduction	Plan long term treatment and a structured response to unavoidable interruption
Body composition	Most loss is fat mass, including visceral fat	Absolute lean mass also decreases; strength and function are rarely measured	Assess protein intake, activity, and functional risk, especially in older adults
Patient reported outcomes	Small average improvements in eating behavior and quality of life; favorable qualitative experiences	Generic scales may miss food preoccupation, stigma, and treatment burden	Use shared decisions and monitor outcomes that matter to the individual
Tolerability	Gastrointestinal events are common and serious events are uncommon in trials	Rare and delayed harms are difficult to estimate	Use gradual escalation, symptom management, and ongoing pharmacovigilance
Emerging agonists	Retatrutide may produce very large loss	Few trials, shorter follow up, limited independent replication	Interpret as promising rather than established comparative superiority

Source: Authors, 2026.

The integrated interpretation indicates that the main uncertainty is no longer whether modern incretin therapies reduce weight. The central questions concern treatment duration, functional tissue preservation, access, and management after interruption.

Table 5. AMSTAR 2 confidence distribution among included reviews

Global confidence	Number of reviews	Interpretation
High	8	Comprehensive searches, explicit risk of bias methods, appropriate synthesis, and consideration of certainty or bias in interpretation
Moderate	5	Generally sound methods with one or more noncritical weaknesses, often limited reporting of excluded studies or overlap
Low	5	Multiple weaknesses or one critical limitation, commonly incomplete search methods, absent protocol, or limited risk of bias integration
Critically low	0	No review was retained when several critical domains were clearly absent

Source: Authors, 2026, using AMSTAR 2 criteria.

High confidence reviews contributed the central numerical estimates. Moderate and low confidence reviews were retained when they addressed outcomes not covered elsewhere, but their findings were used to describe signals and uncertainty rather than to establish definitive comparative conclusions.

3.2 Discussion

The principal finding of this umbrella review is not merely that injectable incretin therapies reduce body weight, but that the magnitude of this effect increases across successive pharmacologic generations while the certainty, durability, and clinical meaning of the loss remain uneven. The drug-specific Cochrane reviews by Meza et al. (2025), Bracchiglione et al. (2025), and Franco et al. (2025) showed a consistent efficacy gradient from liraglutide to semaglutide and tirzepatide. The 2026 network meta-analysis by Nong et al. (2026) reached the same general conclusion, although the absolute estimates were somewhat smaller for semaglutide and tirzepatide than those selected in the present review. This apparent discrepancy is methodological rather than contradictory: the reviews used different comparators, doses, follow-up windows, populations, and network structures. Consequently, the ordering of efficacy appears more robust than any single percentage estimate, and indirect numerical differences should not be interpreted as head-to-head superiority.

The contrast between efficacy and certainty is equally important. Semaglutide and tirzepatide consistently produce larger average reductions than liraglutide, but the Cochrane syntheses also identify substantial industry involvement in the primary evidence base. The semaglutide manufacturer was involved in 17 of 18 included studies, the liraglutide manufacturer in 22 of 24, and all trials included in the tirzepatide review were manufacturer funded (Bracchiglione et al., 2025; Meza et al., 2025; Franco et al., 2025). These facts do not invalidate the observed treatment effects, which are large and internally consistent, but they limit the independence of replication and reinforce the need for longer, pragmatic, and publicly funded comparisons. This concern is even more relevant for retatrutide, for which the estimated weight reductions are striking but are derived from a smaller and less mature evidence base (Misra et al., 2025; Moiz et al., 2025).

The discontinuation literature provides one of the clearest examples of why pooled estimates must be interpreted in context. Berg et al. (2025) reported a mean regain of 2.20 kg after liraglutide and 9.69 kg after semaglutide or tirzepatide, whereas Tzang et al. (2025) estimated a mean regain of 5.63 kg in obesity populations and West et al. (2026) described an average post-cessation increase of approximately 0.4 kg

per month across weight-management medications. These estimates differ substantially in absolute terms, but they converge in direction and are explained by differences in initial weight loss, drug potency, follow-up duration, and eligibility criteria. Berg et al. (2025), in particular, showed that regain was proportional to the weight initially lost. Therefore, greater regain after a more potent agent should not automatically be interpreted as a stronger biological rebound; it partly reflects the larger amount of weight available to be regained.

Budini et al. (2026) add an important temporal dimension to this comparison. Their nonlinear meta-regression suggests that regain is most rapid soon after GLP-1 receptor agonist cessation and subsequently decelerates, whereas the broader modelling by West et al. (2026) estimates a relatively rapid return toward baseline when post-treatment trajectories are averaged over time. Rather than representing competing explanations, the two analyses address different aspects of the same phenomenon: West et al. quantify the average clinical pace of regain, while Budini et al. demonstrate that this pace is not constant. The distinction has practical consequences because a short follow-up may underestimate total regain, whereas a simple linear projection may overstate late regain. Trial extensions such as STEP 1 and SURMOUNT-4, which underpin several of these reviews, similarly show that withdrawal is followed by regain while continued therapy preserves or extends weight reduction (Wilding et al., 2022; Aronne et al., 2024).

The metabolic consequences of withdrawal further argue against viewing regain as a purely cosmetic outcome. Tzang et al. (2025) observed deterioration in glycated hemoglobin, waist circumference, body mass index, blood pressure, and fasting glucose after treatment discontinuation. West et al. (2026) likewise reported that cardiometabolic improvements moved back toward baseline after medication cessation. Taken together, these findings support the interpretation of incretin therapy as chronic disease management rather than a finite course that ends when a target weight is achieved. At the same time, the evidence does not justify assuming that lifelong full-dose therapy is the only acceptable strategy. What remains unknown is whether tapering, lower maintenance doses, switching, or structured behavioral and exercise interventions can preserve a meaningful proportion of the benefit after pharmacologic de-escalation.

The body-composition findings also require reconciliation rather than simple ranking. Karakasis et al. (2025) estimated that approximately one quarter of total weight reduction was attributable to lean mass, and they found that semaglutide 2.4 mg and tirzepatide 15 mg were among the most effective agents for reducing both total weight and fat mass but among the least favorable for preserving absolute lean mass. Bikou et al. (2024), however, reported that the proportion of body weight represented by lean tissue was generally maintained or increased during semaglutide treatment. These results are not mutually exclusive.

Absolute lean mass can fall while relative lean mass increases if fat mass falls to a greater degree. The clinical question is therefore not whether the percentage of lean mass rises, but whether the amount and functional quality of skeletal muscle remain adequate after substantial weight reduction.

The more cautious conclusions of Rochira et al. (2024) regarding tirzepatide illustrate the limits of current evidence. Their review consistently identified reductions in total and visceral fat but considered the data insufficient for firm conclusions about fat-free mass preservation. This contrasts with the more quantitative network synthesis by Karakasis et al. (2025), yet the difference is largely explained by review scope, available trials, and measurement methods. Dual-energy X-ray absorptiometry, bioimpedance, and imaging do not measure identical compartments, and lean mass is not synonymous with skeletal muscle. Accordingly, the present evidence does not support labeling incretin-associated lean-mass reduction as sarcopenia without parallel evidence of impaired strength or performance. Future trials should pair body-composition measures with handgrip strength, chair-rise tests, gait speed, and other functional outcomes, particularly in older adults and people with sarcopenic obesity.

Patient-reported outcomes reveal another important tension between quantitative and qualitative evidence. Pierret et al. (2025) identified small average improvements in several quality-of-life and eating-behavior measures and no clear population-level increase in psychiatric adverse events. In contrast, the qualitative synthesis by Ibsen et al. (2025) describes benefits that patients often experience as highly meaningful, including reduced cravings, less persistent preoccupation with food, improved mobility, and greater participation in daily life. Meanwhile, the Cochrane reviews generally found quality-of-life effects to be small, uncertain, or of limited clinical relevance (Bracchiglione et al., 2025; Franco et al., 2025; Meza et al., 2025). The divergence probably reflects outcome measurement: generic scales dilute individualized changes in hunger, food-related distress, body function, and treatment burden that may be central to the patient's experience.

The mental-health evidence should therefore be interpreted with similar caution. The large meta-analysis by Pierret et al. (2025) is reassuring because it found no clear increase in psychiatric adverse events across more than one hundred thousand participants. However, most psychiatric outcomes were secondary endpoints, and trials often excluded people with severe mental illness, active eating disorders, or complex psychotropic treatment. A population-level absence of signal cannot be translated into absence of risk for every individual. The more defensible clinical implication is to avoid both alarmism and complacency: psychiatric history, eating behavior, mood, and treatment expectations should be assessed when relevant, especially because fear of regain and dependence on continued access may themselves influence psychological well-being.

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Safety findings show a comparatively consistent pattern across review designs. Ismaiel et al. (2025) identified nausea, vomiting, diarrhea, and constipation as the predominant adverse effects in adults without diabetes, while the drug-specific Cochrane reviews reported more treatment withdrawal related to adverse events with incretin therapy than with placebo. Nong et al. (2026) similarly emphasized a benefit-harm trade-off in which greater weight loss is often accompanied by more adverse events and discontinuation. The practical significance is not that the most effective drugs are necessarily less acceptable, but that efficacy rankings cannot be separated from tolerability, dose escalation, and patient preference. Ibsen et al. (2025) showed that many patients were willing to tolerate gastrointestinal symptoms when the perceived benefits were substantial, demonstrating that acceptability is not equivalent to the mere presence or absence of an adverse event.

The distinction between efficacy and real-world effectiveness becomes especially important when these findings are considered together. Randomized trials provide regular follow-up, standardized escalation, and reliable drug supply, whereas clinical practice is affected by cost, shortages, insurance authorization, discontinuation for pregnancy planning, and variable access to multidisciplinary support. A highly efficacious agent may therefore produce a less durable population benefit when continuity is uncertain. This issue also changes the ethical interpretation of regain: when therapy is interrupted because of structural barriers, recurrent weight gain cannot reasonably be framed simply as a failure of adherence or behavior. Continuity of access should be considered part of treatment quality when chronic pharmacotherapy is initiated.

Methodologically, the umbrella design clarifies why the growing number of reviews should not be mistaken for an equivalent number of independent bodies of evidence. The STEP, SCALE, SURMOUNT, and other pivotal programs are repeatedly represented in drug-specific reviews, withdrawal syntheses, network meta-analyses, and safety evaluations. High AMSTAR 2 confidence therefore indicates that a review was conducted rigorously; it does not eliminate dependence created by overlapping primary trials. The decision not to statistically recombine pooled estimates was consequently a strength of the present study, because a second-order meta-analysis would have risked counting the same participants multiple times and producing artificially narrow uncertainty. The trade-off is that the synthesis is interpretive rather than a new pooled estimate, making transparent selection of representative reviews essential.

Several limitations temper the conclusions. Screening and extraction were performed by one reviewer with source verification rather than independent duplicate assessment, and the protocol was not prospectively registered. The search did not include every subscription database, and the degree of primary-study overlap could not be quantified with a formal corrected covered area matrix because several reviews

did not report complete trial-level inclusion tables. Moreover, the evidence is changing rapidly: the most recent network analyses already include emerging agents and combinations that were absent from earlier syntheses, while long-term exposure beyond three to four years remains uncommon. The heavy manufacturer involvement in pivotal trials, underrepresentation of older adults and lower-resource settings, and sparse measurement of muscle function, bone outcomes, and discontinuation strategies further limit generalizability.

These comparisons suggest that the next stage of research should move beyond asking which injection produces the largest mean weight reduction. Head-to-head pragmatic trials should compare maintenance strategies, reduced-dose continuation, tapering, switching, resistance exercise, and nutritional interventions after substantial pharmacologic weight loss. Outcomes should include not only kilograms and percentages, but fat mass, appendicular lean mass, strength, physical function, food preoccupation, treatment burden, access interruptions, and the rate and metabolic consequences of regain. Until such evidence is available, treatment decisions should be framed around a multidimensional concept of success: clinically meaningful adiposity reduction, preserved function, acceptable tolerability, sustainable access, and a realistic plan for maintenance or discontinuation.

4. CONCLUSION

Injectable incretin therapies have established a new level of nonsurgical weight reduction. Liraglutide produces modest average loss, semaglutide produces large loss, and tirzepatide produces still larger loss in current evidence. Retatrutide may extend this range, but its comparative evidence remains less mature. Across agents, the benefit is greatest while treatment continues.

The central limitation is sustainability after withdrawal. Weight regain is common, begins rapidly, and can reverse part of the cardiometabolic improvement. Most weight reduction reflects fat loss, yet a meaningful amount of lean tissue is also lost, while evidence on muscle function remains inadequate. Gastrointestinal effects are common and increase discontinuation, whereas serious adverse events are uncommon in randomized trials but require continued surveillance.

High quality obesity care should therefore move beyond a single efficacy estimate. Treatment selection should consider the expected magnitude of loss, capacity for continued access, individual tolerance, muscle and nutritional risk, patient reported benefits, and a plan for maintenance or interruption. The most important next step is not merely to produce a more potent injection, but to establish how substantial weight loss can be maintained safely, functionally, and equitably over the long term.

ETHICAL ASPECTS

Ethics committee approval was not applicable because this study synthesized published and publicly available literature and did not involve direct contact with human participants or access to identifiable data.

DATA AVAILABILITY

All data supporting the conclusions are reported in the manuscript and can be traced to the cited systematic reviews. The structured extraction matrix may be provided to the journal during peer review.

REFERENCES

AROMATARIS, E. et al. Chapter 10: Umbrella reviews. In: AROMATARIS, E.; LOCKWOOD, C.; PORRITT, K.; PILLA, B.; JORDAN, Z. (ed.). **JBI manual for evidence synthesis**. Adelaide: Joanna Briggs Institute, 2024. DOI: 10.46658/JBIMES-24-09.

ARONNE, L. J. et al. Continued treatment with tirzepatide for maintenance of weight reduction in adults with obesity: the SURMOUNT-4 randomized clinical trial. **JAMA**, v. 331, n. 1, p. 38-48, 2024. DOI: 10.1001/jama.2023.24945.

BERG, S. et al. Discontinuing glucagon-like peptide-1 receptor agonists and body habitus: a systematic review and meta-analysis. **Obesity Reviews**, v. 26, n. 8, e13929, 2025. DOI: 10.1111/obr.13929.

BIKOU, A. et al. A systematic review of the effect of semaglutide on lean mass: insights from clinical trials. **Expert Opinion on Pharmacotherapy**, v. 25, n. 5, p. 611-619, 2024. DOI: 10.1080/14656566.2024.2343092.

BRACCHIGLIONE, J. et al. Semaglutide for adults living with obesity. **Cochrane Database of Systematic Reviews**, n. 10, CD015092, 2025. DOI: 10.1002/14651858.CD015092.pub2.

BUDINI, B. et al. Trajectory of weight regain after cessation of GLP-1 receptor agonists: a systematic review and nonlinear meta-regression. **EClinicalMedicine**, v. 93, 103796, 2026. DOI: 10.1016/j.eclinm.2026.103796.

DAMEN, J. A. A. et al. Benefits and harms of pharmacologic treatments in adults with overweight or obesity: a living systematic review and network meta-analysis for the American College of Physicians. **Annals of Internal Medicine**, 2026. Advance online publication. DOI: 10.7326/ANNALS-24-03764.

FRANCO, J. V. A. et al. Tirzepatide for adults living with obesity. **Cochrane Database of Systematic Reviews**, n. 10, CD016018, 2025. DOI: 10.1002/14651858.CD016018.

GATES, M. et al. Reporting guideline for overviews of reviews of healthcare interventions: development of the PRIOR statement. **BMJ**, v. 378, e070849, 2022. DOI: 10.1136/bmj-2022-070849.

IBSEN, C. K. et al. Patients' experiences with GLP1-RAs: a systematic review. **Scandinavian Journal of Primary Health Care**, v. 43, n. 2, p. 370-379, 2025. DOI: 10.1080/02813432.2025.2477141.

ISMAIEL, A. et al. Gastrointestinal adverse events associated with GLP-1 RA in non-diabetic patients with overweight or obesity: a systematic review and network meta-analysis. **International Journal of Obesity**, v. 49, p. 1946-1957, 2025. DOI: 10.1038/s41366-025-01859-6.

JASTREBOFF, A. M. et al. Tirzepatide once weekly for the treatment of obesity. **New England Journal of Medicine**, v. 387, n. 3, p. 205-216, 2022. DOI: 10.1056/NEJMoa2206038.

JASTREBOFF, A. M. et al. Triple-hormone-receptor agonist retatrutide for obesity: a phase 2 trial. **New England Journal of Medicine**, v. 389, n. 6, p. 514-526, 2023. DOI: 10.1056/NEJMoa2301972.

KARAKASIS, P. et al. Effect of glucagon-like peptide-1 receptor agonists and co-agonists on body composition: systematic review and network meta-analysis. **Metabolism**, v. 164, 156113, 2025. DOI: 10.1016/j.metabol.2024.156113.

KOLLI, R. T. et al. Rebound or retention: a meta-analysis of weight regain after the discontinuation of GLP-1 receptor agonists and other anti-obesity drugs. **Cureus**, v. 17, n. 10, e94926, 2025. DOI: 10.7759/cureus.94926.

MEZA, N. et al. Liraglutide for adults living with obesity. **Cochrane Database of Systematic Reviews**, n. 10, CD016017, 2025. DOI: 10.1002/14651858.CD016017.

MISRA, S.; NARAYAN, R. K.; KAUR, M. Efficacy and safety of retatrutide for the treatment of obesity: a systematic review of clinical trials. **Journal of Basic and Clinical Physiology and Pharmacology**, v. 36, n. 4, p. 263-274, 2025. DOI: 10.1515/jbcpp-2025-0113.

MOIZ, A. et al. Efficacy and safety of glucagon-like peptide-1 receptor agonists and coagonists for the treatment of obesity among adults without diabetes: a systematic review of randomized controlled trials. **Annals of Internal Medicine**, v. 178, n. 2, p. 199-217, 2025. DOI: 10.7326/ANNALS-24-01590.

NONG, K. et al. Comparative effects of drugs for adults with overweight or obesity: systematic review and network meta-analysis. **BMJ**, v. 394, e372161, 2026. DOI: 10.1136/bmj-2026-372161.

PAGE, M. J. et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. **BMJ**, v. 372, n71, 2021. DOI: 10.1136/bmj.n71.

PIERRET, A. C. S. et al. Glucagon-like peptide-1 receptor agonists and mental health: a systematic review and meta-analysis. **JAMA Psychiatry**, 2025. DOI: 10.1001/jamapsychiatry.2025.0679.

ROCHIRA, V. et al. The effect of tirzepatide on body composition in people with overweight and obesity: a systematic review of randomized controlled studies. **Diseases**, v. 12, n. 9, 204, 2024. DOI: 10.3390/diseases12090204.

RODRIGUEZ, P. J. et al. Semaglutide vs tirzepatide for weight loss in adults with overweight or obesity. **JAMA Internal Medicine**, v. 184, n. 9, p. 1056-1064, 2024. DOI: 10.1001/jamainternmed.2024.2525.

SATTAR, N. et al. Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of randomised trials. **The Lancet Diabetes & Endocrinology**, v. 9, n. 10, p. 653-662, 2021. DOI: 10.1016/S2213-8587(21)00203-5.

SHEA, B. J. et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. **BMJ**, v. 358, j4008, 2017. DOI: 10.1136/bmj.j4008.

TZANG, C. C. et al. Metabolic rebound after GLP-1 receptor agonist discontinuation: a systematic review and meta-analysis. **EClinicalMedicine**, v. 90, 103680, 2025. DOI: 10.1016/j.eclinm.2025.103680.

WEST, S. et al. Weight regain after cessation of medication for weight management: systematic review and meta-analysis. **BMJ**, v. 392, e085304, 2026. DOI: 10.1136/bmj-2025-085304.

WILDING, J. P. H. et al. Once-weekly semaglutide in adults with overweight or obesity. **New England Journal of Medicine**, v. 384, n. 11, p. 989-1002, 2021. DOI: 10.1056/NEJMoa2032183.

WILDING, J. P. H. et al. Weight regain and cardiometabolic effects after withdrawal of semaglutide: the STEP 1 trial extension. **Diabetes, Obesity and Metabolism**, v. 24, n. 8, p. 1553-1564, 2022. DOI: 10.1111/dom.14725.

WORLD HEALTH ORGANIZATION. **Guideline on the use of glucagon-like peptide-1 receptor agonists in adults living with obesity**. Geneva: World Health Organization, 2025.

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APPENDIX A. SEARCH STRATEGIES

The search was updated on July 23, 2026. Syntax was adapted to each source. The PubMed strategy below is provided in full; equivalent concepts were used in the other sources.

Source	Search logic
PubMed	("Obesity"[Mesh] OR obes*[Title/Abstract] OR overweight[Title/Abstract]) AND ("Glucagon Like Peptide 1 Receptor Agonists"[Mesh] OR GLP-1[Title/Abstract] OR incretin*[Title/Abstract] OR liraglutide[Title/Abstract] OR semaglutide[Title/Abstract] OR tirzepatide[Title/Abstract] OR retatrutide[Title/Abstract]) AND (systematic review[Publication Type] OR meta-analysis[Publication Type] OR systematic review[Title/Abstract] OR meta analysis[Title/Abstract])
Cochrane Library	(obesity OR overweight) AND (GLP 1 OR incretin OR liraglutide OR semaglutide OR tirzepatide OR retatrutide) in Title Abstract Keyword, restricted to Cochrane Reviews
Epistemonikos	(obesity OR overweight) AND (GLP 1 OR semaglutide OR tirzepatide OR liraglutide OR retatrutide), filtered to systematic reviews
Google Scholar	Allintitle combinations of obesity, GLP 1, semaglutide, tirzepatide, retatrutide, systematic review, meta analysis, withdrawal, body composition, and quality of life; the first 200 results sorted by relevance and recent year were inspected

Source: Authors, 2026.

Citation tracking was performed from included reviews, the most recent Cochrane reviews, and the 2026 living network meta analyses. Records were assessed against the same eligibility criteria regardless of retrieval source.