Systematic Review

Emerging Anti-Obesity Medications for Obesity Management: A Systematic Review of Efficacy, Safety, and Outcomes

Kishna Ram[1], Syed Haris Bukhari[1], Rahul Arora[2], Neena Katoch[3], Rachna Gulati[4]

[1]Assistant Professor, Department of Pharmacology, Geetanjali Medical College and Hospital, Udaipur, Rajasthan, India. [2]Associate Professor, NIIMS, Greater Noida, Uttar Pradesh, India. [3]Associate Professor, Department of Pharmacology, Geetanjali Medical College and Hospital, Udaipur, Rajasthan, India. [4]Associate Professor, Department of Pathology, SGT Medical College and Hospital, Gurgaon, Haryana, India

Abstract

Background: The systematic review was done with an objective to assess efficacy and safety of anti-obesity medications (AOMs), FDA-approved and emerging, in various populations (older than 50 years of age, children, and individuals with type 2 diabetes [T2DM]); and to analyze cardiometabolic outcomes. **Material and Methods:** A detailed search was performed on several databases such as PubMed, Web of Science, DOAJ, Scopus and Embase, resulting in more than 7,000 potential citations. The inclusion criteria of the eight systematic reviews/meta-analyses were met and included hundreds of RCTs and real-world evidence studies. The data extracted included adverse event (AE) profiles, body weight changes and cardiometabolic outcomes. **Results:** All the pharmacological interventions showed better weight loss than the placebo treatment. Tirzepatide was the best of the drugs approved to date for absolute weight loss (WMD - 11.69 kg), whereas pipeline triple-agonist retatrutide had the highest mean weight loss (X WMD - 24.2% mean weight loss). The oral treatments included were orforglipron, which resulted in -14.7% weight loss at 36 weeks. The older adults ≥65 years old had significant reductions with semaglutide (8.1%). Cardiometabolic benefits were seen with tirzepatide's ability to lower systolic blood pressure by 5.74 mmHg and HbA1c by 1.27%. Gastrointestinal AEs occurred and were common, though: There was a higher risk of vomiting with tirzepatide (RR 4.95), and diarrhea was reported in 41% of participants in trials of semaglutide. **Conclusion:** Modern AOMs, notably GLP-1 and multi-receptor agonists like tirzepatide and retatrutide, achieve superior weight loss and significant cardiometabolic benefits across diverse populations. While highly efficacious, gastrointestinal side effects are common and often hinder real-world persistence.

Keywords: Cardiovascular diseases, orlistat, obesity management, semaglutide, weight loss.

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Introduction

Excess weight and obesity, the build-up of fat that is not normal, are an epidemic in the world affecting peoples' health and wellbeing. High BMI is associated with increased risk of cardiometabolic diseases.[1-3] It causes 4.0 million deaths worldwide, 2+3 of which takes place in the form of cardiovascular deaths such as heart failure and coronary heart disease.[1-3]

The use of anti-obesity medications (AOMs) has held significant safety concerns; for example, fenfluramine was linked to valvular heart disease, and rimonabant was suspended due to severe risks of depression and anxiety.[4,5] However, pharmacotherapy has advanced significantly, shifting from appetite suppressants to agents that modulate hormonal and metabolic pathways.[6]

Newer therapies are being introduced for preventing obesity, which include GLP-1 receptor agonists like semaglutide and liraglutide, and the novel dual GIP/GLP-1 receptor co-agonist, tirzepatide.[7,8] Furthermore, the pipeline is expanding with next-generation triple agonists, such as retatrutide, orforglipron, CagriSema, survodutide, and danuglipron, which target multiple receptors to enhance metabolic efficiency.[9]

Following the recent approval of these potent medications, interest in comparing their safety profiles and efficacy across diverse dimensions has rapidly increased. Thus, it becomes important to understand safety and efficacy of these therapies for anti-obesity and their results. Thus, a systematic review and meta-analysis was done, which aims to fill that gap by summarizing recent systematic reviews on these pharmacotherapies and its effectiveness in weight reduction and preventing the cardiometabolic adverse outcomes with a comparison of the side-effects associated with different medications.

Materials and Methods

This systematic review was conducted in strict adherence to the Preferred Reporting Items for Systematic Reviews and Meta-

Address for correspondence: Dr. Neena Katoch, Associate Professor, Department of Pharmacology, Geetanjali Medical College and Hospital, Udaipur, Rajasthan, India
E-mail: drneenakatoch@gmail.com

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Analyses (PRISMA 2020) statement and checklist to ensure a transparent and comprehensive reporting of the methodology and results.[10]

Search Strategy and Data Sources

A comprehensive and systematic literature search was performed across multiple electronic databases, including PubMed, Web of Science, DOAJ, Scopus, and Embase. To capture the most relevant and contemporary evidence, the search was restricted to the last 5 years (2021–2026), on systematic reviews published in English and freely downloadable. Additionally, forward and backward citation chasing (citation searching) was performed to identify any relevant studies missed by the initial database query.

The search employed a combination of Medical Subject Headings (MeSH) terms and free-text keywords related to obesity and newer pharmacotherapies. The specific keywords utilized in the search strings included: ("obesity" OR "overweight" OR "weight loss" OR "weight reduction" OR "body weight") AND ("Drug Therapy" OR "Pharmacotherapy" OR "Pharmaceutical Preparations") AND ("glucagon-like peptide-1 receptor agonists" OR "GLP-1 RA" OR "semaglutide" OR "liraglutide" OR "tirzepatide" OR "retatrutide" OR "triple agonist" OR "GIP/GLP-1 co-agonist").

Inclusion and Exclusion Criteria

Studies were selected based on the following inclusion criteria:

1. **Study Design:** Systematic reviews were included to provide the highest level of evidence for efficacy and safety.
2. **Population:** Adults (≥18 years) with a diagnosis of overweight or obesity, defined by a body mass index (BMI) ≥30 kg/m² or BMI ≥27 kg/m² with at least one weight-related comorbidity (e.g., type 2 diabetes, hypertension, or CVD).
3. **Interventions:** Pharmacotherapies approved by regulatory bodies like the FDA or EMA, specifically focusing on GLP-1 receptor agonists (semaglutide, liraglutide), dual agonists (tirzepatide), and emerging triple agonists (retatrutide).
4. **Comparators:** Controlled trials must have included a placebo control or an active comparator.
5. **Outcomes:** Reporting of at least one primary efficacy endpoint, such as percentage change in total body weight from baseline, or safety endpoints, such as serious adverse events or discontinuation rates.

Exclusion criteria:

- Observational studies, randomized or non-randomised studies, animal models, and case reports.
- Studies involving pregnant women or individuals with monogenic/syndromic obesity.
- Trials with duration of less than 12 weeks to ensure meaningful assessment of weight loss maintenance.
- Studies with insufficient or unavailable data

Study Selection and Screening

The retrieved citations were assessed for the removal of duplicates. The remaining records underwent a two-step screening process:

1. Title and Abstract Screening: Two independent reviewers screened titles and abstracts to identify potentially relevant studies based on the predefined criteria.
2. Full-Text Review: The full texts of the selected studies were retrieved and independently assessed for eligibility.

Any discrepancies during the screening and selection phases were resolved through discussion and consensus or by consultation with a third senior investigator. The study selection process is summarized in the PRISMA flow chart (Figure 1).

Data Extraction: Data were independently extracted by two reviewers using a standardized Microsoft Excel template. The following information was recorded:

- **Study Characteristics:** Author, publication year, trial name, and geographic location.
- **Population Demographics:** Sample size, mean age, sex distribution, and baseline BMI/waist circumference.
- **Intervention Details:** Drug name, class, dose, frequency, and treatment duration.
- **Outcome Measures:** Mean percentage weight loss, proportion of patients achieving ≥5%, ≥10%, or ≥15% weight reduction, and changes in cardiometabolic markers (e.g., HbA1c, blood pressure, lipid profile).
- **Safety Data:** Incidence of adverse events (AEs), serious adverse events (SAEs), and reasons for treatment discontinuation.

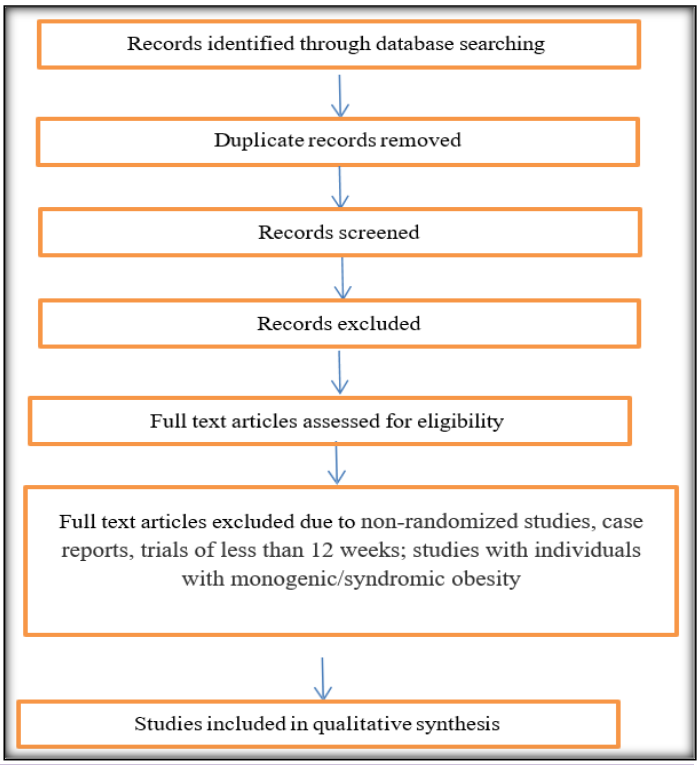

Figure 1: PRISMA flow diagram

Results

This systematic review synthesizes evidence from eight recent systematic reviews and meta-analyses to evaluate the efficacy and safety of current and emerging pharmacological interventions for weight loss.

Of the initial 7,646 potential articles identified through database

searches, 238 citations met the criteria for full-text review following the removal of duplicates and initial title/abstract screening.[8,11] Subsequently, eight systematic reviews and meta-analyses met the inclusion criteria. [Table 1]

Table 1: Overview of systematic reviews assessing the efficacy and safety of AOMs

Author	Year	Number of Studies	Population and Drugs Studied	Outcome Parameters	Results
Ahmad et al,[12]	2021	41 studies	Population: Real-world patients with obesity. Drugs: FDA-approved AOMs (Phentermine, Orlistat, Liraglutide, Naltrexone/Bupropion, etc.).	Absolute/Percenta ge Weight Change	Phentermine+ lifestyle program achieved weight loss of −15.1% at 12 weeks and −18.9% at 26 weeks. Liraglutide (3.0 mg): −6.0 kg at ≥16 weeks and −7.4 kg at ≥28 weeks. Orlistat: −4.09 kg at 6 months to −10.8 kg at 6–9 months.
				Categorical Weight Loss (≥5%)	Orlistat: 46.3% achieved >5% weight loss. Liraglutide: 56.5% achieved >5% weight loss at 3–6 months, increasing to 64.7% by the end of follow-up.
				Adherence and Discontinuation	Orlistat: 30.3% discontinued within the first 3 months; 47.5% by 6 months. Liraglutide: 20% discontinued after a median of 108 days. Persistence at 1 year: Liraglutide 61%, Orlistat 46.8%.
Alshahrani et al,[13]	2024	25 RCTs	Population: Patients with type 2 diabetes mellitus (T2DM) and obesity. Drugs: GLP-1 receptor agonists, SGLT2 inhibitors, Metformin, Phentermine/Topiramate.	Glycemic Control (HbA1c/FSG)	Cotadutide (200 µg): Significant reductions in HbA1c at 6 weeks. Dulaglutide: Fasting serum glucose assessed across doses of 1.5–4.5 mg.
				Body Weight and Composition	Semaglutide (2.4 mg): Least-square mean reductions in total body fat mass, body weight, lean mass, and waist circumference at 48 weeks.
				Adverse Events (TEAEs)	Diarrhea occurred in 41% of semaglutide-treated patients. Nausea occurred in 72% receiving cotadutide and 30.3% receiving high-dose dulaglutide (4.5 mg).
Chen et al,[11]	2025	8 studies	Population: Adults aged ≥65 years with obesity. Drugs: Semaglutide, Tirzepatide, Liraglutide, Orlistat, etc.	Weight Reduction in Older Adults (≥65 years)	Semaglutide: −8.1% weight loss in adults aged 65–75 years and −7.49% in adults ≥75 years over 59 months. Tirzepatide: −22% weight change at 72 weeks versus −3.8% with placebo. Orlistat: −8.4% body weight reduction over 24 weeks.
				Odds of Success (≥5% Weight Loss)	Adults aged ≥65 years had 3.8-fold higher odds (95% CI: 1.2–12.4) of achieving ≥5% weight loss compared with adults <40 years.
Kokkorakis et al,[14]	2025	57 trials/report s	Population: Non-diabetic adults with obesity. Drugs: Thirty-six Pipeline drugs (Retatrutide, Ecnoglutide, CagriSem, AMG 133, etc.).	Pipeline Efficacy (Body Weight Change)	Retatrutide (Phase 2): Least-square mean weight changes ranged from −8.7% (1mg) to −24.2% (12mg) at 48 weeks. Beloranib: −5.5kg (0.6 mg) to −10.9 kg (2.4mg) over 12 weeks.
				Pipeline Efficacy (Categorical)	HS-20094: Primary outcome is the proportion of patients achieving ≥5% weight reduction over 24 weeks (ongoing trial).
Liu et al,[15]	2025	154 studies	Population: Overweight or obese individuals.	Cardiometabolic Outcomes (HOMA-IR)	Orlistat: WMD−1.56; Tirzepatide: WMD−0.35;

			Drugs: 10 AOMs (Tirzepatide, Semaglutide, Liraglutide, Orlistat, etc.).		Naltrexone: WMD−6.10 for insulin resistance.
				Safety and Side Effects	Diarrhea risk: Orlistat RR 2.20; Semaglutide RR 1.60. Acute pancreatitis with semaglutide: RR 0.71. Tirzepatide reduced osteoarthritis risk (RR 0.66).
Misra et al,[16]	2025	3 articles	Population: 691 randomized patients; average age 54.26 years Drug: Retatrutide	Body weight, BMI, waist circumference, categorical weight loss (≥5% to 20%), and safety	Efficacy: 12 mg dose showed most significant reductions in weight, BMI, and WC. Higher percentage of patients achieved weight losses of ≥5%, 10%, 15%, and 20% vs. placebo. Safety: Gastrointestinal adverse effects were most common
Benedictus et al,[17]	2025	18 RCTs	Population: 12,259 patients with obesity Drugs: Oral medications (Phentermine/ Topiramate, Semaglutide, Naltrexone/Bupropion, Orlistat, etc.)	Comparative weight loss (Mean Difference [MD]) vs. placebo	Weight Loss (MD): Phentermine/topirama te (-3.28), Semaglutide (-2.92), phentermine (-2.31), naltrexone/bupropion (-1.68), and orlistat (-1.44). Overall MD for oral therapies vs. placebo was -2.12
Zhou et al,[18]	2025	21 RCTs	Population: 2,186 children with obesity Drugs: Orlistat, GLP-1RA (liraglutide, semaglutide), Phentermine/Topiramat e	Weight loss (BW, BMI), LDL-C, blood glucose, and related adverse events	Efficacy: Orlistat 6-month BMI SMD was -0.34. GLP-1RA 12-month BMI SMD was -0.39. Phentermine/topirama te MD was -3.9% weight loss. Safety: Orlistat increased oily bowel risk (RR 6.35) and fecal incontinence (RR 12.39)

Weight reduction outcomes: Pharmacological interventions consistently demonstrated superior weight loss compared to placebo. Tirzepatide was identified as the most effective FDA-approved agent for absolute weight loss (WMD -11.69 kg), followed by semaglutide (WMD -8.48 kg).[15] In a meta-analysis of oral medications, phentermine/topiramate achieved the greatest mean difference (MD -3.28) compared to other oral options like naltrexone/bupropion (MD -1.68) and orlistat (MD -1.44).[17] Pipeline investigations highlighted the potency of retatrutide, a triple agonist, which achieved a maximum mean weight loss of 24.2% at 48 weeks in phase 2 trials.[16]

For childhood obesity, real-world data also demonstrated weight loss with different agents, although to a smaller degree than in clinical trials, ranges between 14% to 58.6% with a clinically meaningful reduction of ≥5%, resulting in an SMD ranging from -1.17 to -3.63.12 Weight loss occurred with each of the GLP-1RAs (SMD -0.39; after 12 months) and with orlistat (SMD -0.34; after 6 months).

Outcomes related to cardiometabolic and quality of life: AOMs delivered significant cardiometabolic benefits. cardiovascular outcomes were also significant with tirzepatide (-5.74 mm Hg) and semaglutide (-1.27%) having the greatest antihypertensive and glucose-lowering effects, respectively, while cardiovascular safety was noteworthy (tirzepatide reduced MACE by 17% and liraglutide reduced MACE by 13%).[15] psychological outcomes varied such that IWQOL-Lite total score improved by WMD 10.06 and 7.96 with tirzepatide and semaglutide, respectively. On the other hand, phentermine/topiramate had a higher risk of anxiety (RR 1.91) and sleep disorder (RR 1.55).[15]

Safety and persistence: Gastrointestinal (GI) adverse events were the most frequently reported safety concerns across all drug classes.[13,16] Tirzepatide was associated with the highest risk of vomiting (RR 4.95), while liraglutide carried the highest risk for diarrhea (RR 1.64).15 In pediatric trials, orlistat significantly increased the risk of oily bowel movements (RR 6.35) and fecal incontinence (RR 12.39).[18]

Real-world evidence highlighted a significant gap in adherence and persistence.[12] Approximately 47.5% of orlistat users discontinued treatment by 6 months, often citing side effects or perceived lack of effectiveness.[12] In contrast, liraglutide demonstrated higher real-world persistence (61% at 1 year).[12]

Discussion

The field of AOMs has shifted from simple appetite suppressants to sophisticated agents modulating hormonal and metabolic pathways.5 GLP-1 receptor agonists (RAs), such as semaglutide and liraglutide, mimic incretin hormones to reduce appetite, enhance satiety, and delay gastric emptying by acting on the central nervous system.[14] Tirzepatide functions as a dual GIP and GLP-1 receptor co-agonist, further enhancing glucose-dependent insulin secretion and metabolic efficiency.[15] Emerging triple agonists like retatrutide target GLP-1, GIP, and glucagon receptors, potentially achieving bariatric-level weight loss by increasing energy expenditure and fat oxidation.[14] In contrast, orlistat works peripherally by inhibiting gastric and pancreatic lipases, reducing dietary fat absorption by approximately 30%.[5] Centrally acting combinations like phentermine/topiramate suppress appetite through neurotransmitter modulation and g-aminobutyric acid (GABA) receptor stimulation.[14]

It is important to note that lifestyle modification is the foundation

of obesity treatment and that lifestyle modifications can be enhanced with the use of AOMs.[5] Lifestyle changes by themselves are shown to be less successful for maintaining lost weight in the real world than when combined with the use of these medications.[13] Lifestyle modifications alone or in combination with a specific type of medication, such as the newer AOMs, can help increase likelihood of maintaining lost weight.

Patients with established CVD should be more selective regarding the use of obesity medications that have been shown to reduce major adverse cardiovascular events (MACE) such as semaglutide and liraglutide, whereas those with metabolic dysfunction-associated steatotic liver disease (MASLD) might respond better to dual agonist drugs that additionally contain glucagon as a target, such as efinopegdutide, and also target liver fat oxidation directly. Moreover, newer agents such as bimagrumab are being evaluated to address fat reduction without a loss of lean muscle mass in an important question in older individuals.5 Subcutaneous GLP-1 RAs are potent, but are often accompanied by GIT side effects (such as nausea and vomiting) in clinical practice.[11,14] Oral semaglutide reproduces these effects but requires strict administration on an empty stomach with limited water.[5,14] In contrast, the novel oral non-peptide orforglipron provides similar efficacy without these restrictive dosing requirements.[5,14] Centrally acting oral therapies like phentermine/topiramate carry unique risks, including insomnia, anxiety, and cognitive impairment, which are less prevalent with injectable incretin-based therapies.[11,15]

A primary limitation of the current evidence is that the long-term safety and efficacy of newer agents beyond trial periods remain unknown.[13,14] Potential risks, such as thyroid C-cell tumors, acute kidney injury, and the impact of significant bone and muscle mass loss, require further longitudinal study.[14] Additionally, real-world data highlights significant challenges with adherence and weight regain following drug discontinuation, emphasizing that obesity often requires lifelong management.

Conclusion

Modern AOMs, notably GLP-1 and multi-receptor agonists like tirzepatide and retatrutide, achieve superior weight loss and significant cardiometabolic benefits across diverse populations. While highly efficacious, gastrointestinal side effects are common and often hinder real-world persistence. Emerging oral therapies offer promising alternatives to injectables. Ultimately, while modern AOMs represent a paradigm shift in obesity management, future research must focus on long-term safety and improving adherence to bridge the gap between clinical trial success and sustainable real-world outcomes.

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Conflicts of interest

There are no conflicts of interest.

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