INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES
[ISSN: 0975-4725; CODEN(USA): IJPS00]
Journal Homepage: https://www.ijpsjournal.com

OPEN ACCESS

Research Article

Meta Analysis of FDA Approved Weight Loss Drugs in Obesity

Jessy Jayakumar[1], Chandini[2], Marka Sheshi[3], Srujana Rani Kasoju[4],Talla Sairam Goud[5]

[1]*Pharm.D Graduate, JKKN College of Pharmacy, TamilNadu Dr. M.G.R Medical University, Chennai.*
[2]*Doctor of pharmacy ,Department of pharmacy practice, St.Peters Institute of Pharmaceutical Sciences, Kakatiya university, Hanamkonda,506001,Telangana, India*
[3]*Doctor of Pharmacy, Department of Pharmacy Practice, St. Peter's Institute of Pharmaceutical Sciences, Kakatiya University, Hanamkonda,506001, Telangana, India*
[4]*Department of Pharmacy Practice, St. Peter's Institute of Pharmaceutical Sciences, Kaktiya University, Hanmakonda, 506001, Telangana, India.*
[5]*Department of Pharmacy Practice, KVK College Of Pharmacy, Jawaharlal Nehru Technological University,Surmaiguda, Ranga Reddy, 501512, Hyderabad, Telangana, India*

ARTICLE INFO

Published: 3 Aug. 2026
Keywords:
obesity; FDA-approved drugs; pharmacotherapy; meta-analysis; weight loss; GLP-1 agonists; semaglutide; tirzepatide; orlistat; systematic review .
DOI:
10.5281/zenodo.21771494

ABSTRACT

Obesity is a global chronic disease affecting over 1 billion adults, conferring significant morbidity and mortality through associated cardiometabolic comorbidities. Pharmacotherapy represents a critical adjunct to lifestyle modification, and the past two decades have witnessed substantial expansion in the US Food and Drug Administration (FDA)-approved anti-obesity medications (AOMs). Despite advances, comparative evidence across approved agents remains fragmented, underscoring the need for a rigorous systematic synthesis. To systematically review and meta-analyse the efficacy, safety, tolerability, and cardiometabolic outcomes of all currently FDA-approved weight-loss medications in adults with obesity or overweight with comorbidities. A systematic search of PubMed, EMBASE, CENTRAL, and ClinicalTrials.gov was conducted from database inception through December 2025. Randomised controlled trials (RCTs) of ⩾12 weeks' duration evaluating orlistat, phentermine/topiramate ER, bupropion/naltrexone ER, liraglutide 3.0 mg, semaglutide 2.4 mg, or tirzepatide in adults with BMI ⩾30 kg/m² or ⩾27 kg/m² with at least one weight-related comorbidity were included. Primary outcomes were mean percentage body weight change and proportion of participants achieving ⩾5% weight loss from baseline. Secondary outcomes included ⩾10% and ⩾15% weight loss thresholds, change in waist circumference, HbA1c, blood pressure, lipids, and adverse event profiles. Randomeffects meta-analysis using DerSimonian-Laird methodology was

***Corresponding Author:** Jessy Jayakumar
Address: *Pharm.D Graduate, JKKN College of Pharmacy, TamilNadu Dr. M.G.R Medical University, Chennai*
Email ✉: quamruz.bcp@gmail.com

Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

employed. Risk of bias was assessed using the Cochrane RoB 2.0 tool. Heterogeneity was quantified using I^2 statistics. Sixty-two RCTs (n = 49,387 participants) met inclusion criteria. Among approved AOMs, tirzepatide 15 mg demonstrated the greatest mean percentage weight loss (−20.9%, 95% CI −22.1 to −19.7%), followed by semaglutide 2.4 mg (−14.9%, 95% CI −16.0 to −13.8%), phentermine/topiramate ER (−9.3%, 95% CI −10.4 to −8.2%), bupropion/naltrexone ER (−5.0%, 95% CI −6.0 to −4.0%), liraglutide 3.0 mg (−6.2%, 95% CI −7.0 to −5.4%), and orlistat (−2.9%, 95% CI −3.6 to −2.2%). The proportion of participants achieving ≥5% body weight loss ranged from 22.8% (orlistat) to 91.0% (tirzepatide). GLP-1 receptor agonists and dual GIP/GLP-1 agonists demonstrated significant cardiometabolic benefits including reductions in HbA1c, systolic blood pressure, triglycerides, and cardiovascular event rates. Gastrointestinal adverse events were the most common across GLP-1-based therapies (30–50%), while orlistat exhibited predominantly gastrointestinal steatorrhoea. Overall study heterogeneity was moderate (I^2 range 18–58%). Newer incretin-based therapies, particularly semaglutide 2.4 mg and tirzepatide, represent a paradigm shift in obesity pharmacotherapy, achieving clinically meaningful weight reduction previously attainable only through bariatric surgery. Drug selection must be individualised, considering efficacy goals, comorbidity profile, tolerability, cost, and cardiovascular risk. Future comparative effectiveness research and long-term safety surveillance are imperative.

INTRODUCTION

Obesity, defined by the World Health Organization (WHO) as a body mass index (BMI) ≥30 kg/m², represents one of the most pressing global public health crises of the twenty-first century. In 2024, the WHO estimated that more than 1 billion individuals worldwide live with obesity, a figure that has more than tripled since 1975 [1]. In the United States alone, the age-adjusted prevalence of obesity among adults reached 41.9% in 2022, with severe obesity (BMI ≥40 kg/m²) affecting 9.2% of the population [2].

The pathophysiology of obesity is multifactorial, involving complex interactions between genetic predisposition, neuroendocrine regulation of appetite and energy expenditure, gut microbiome composition, environmental determinants, and psychosocial factors [3]. Obesity is not merely a cosmetic or lifestyle condition; it is a chronic, relapsing neurobehavioural disease causally associated with over 200 medical comorbidities, including type 2 diabetes mellitus (T2DM), hypertension, dyslipidaemia, obstructive sleep apnoea, non-alcoholic fatty liver disease (NAFLD), polycystic ovary syndrome (PCOS), osteoarthritis, and multiple cancers [4]. The direct and indirect economic burden of obesity in the United States has been estimated to exceed $1.72 trillion annually [5].

The cornerstone of obesity management remains lifestyle intervention encompassing dietary modification, physical activity, and behavioural counselling. However, long-term adherence to lifestyle measures is challenging, and the biological adaptation to caloric restriction — characterised by compensatory reductions in resting metabolic rate and increases in orexigenic hormone signalling — frequently culminates in weight regain [6]. Pharmacotherapy provides a biologically rational adjunct to lifestyle modification by targeting the neuroendocrine mechanisms underpinning energy homeostasis.

The history of FDA-approved anti-obesity medications (AOMs) is marked by both therapeutic advances and regulatory withdrawals driven by safety concerns. Amphetamine-derived appetite suppressants were largely withdrawn due to cardiovascular toxicity and abuse potential. Fenfluramine and dexfenfluramine were withdrawn in 1997 following reports of cardiac valvulopathy and primary pulmonary hypertension [7]. Sibutramine was withdrawn in 2010 following the SCOUT trial, which demonstrated increased cardiovascular event rates [8]. Rimonabant, a cannabinoid-1 receptor antagonist approved in

Europe but rejected by the FDA, was withdrawn due to psychiatric adverse events including depression and suicidality [9].

Against this backdrop of historical withdrawals, the contemporary landscape of FDA-approved weight management pharmacotherapy has evolved substantially. As of 2025, six agents hold FDA approval specifically for chronic weight management in adults: orlistat (1999), phentermine/topiramate extended-release (2012), bupropion/naltrexone extended-release (2014), liraglutide 3.0 mg (2014), semaglutide 2.4 mg (2021), and tirzepatide (2023) [10]. The emergence of glucagon-like peptide-1 (GLP-1) receptor agonists and dual glucosedependent insulinotropic polypeptide (GIP)/GLP-1 agonists has fundamentally transformed the therapeutic paradigm, delivering weight reductions previously achievable only through bariatric surgical intervention [11].

Despite this landscape, clinicians face challenges in selecting appropriate pharmacotherapy. No prior meta-analysis has comprehensively compared all six FDA-approved AOMs simultaneously with respect to efficacy across standardised outcome thresholds, safety profiles, and cardiometabolic outcomes. This systematic review and meta-analysis aims to address this gap by synthesising evidence from randomised controlled trials (RCTs) published through December 2025, providing a rigorous comparative framework to guide evidence-based clinical decision-making.

METHODS

Protocol and Registration

This systematic review and meta-analysis was conducted in accordance with the Preferred Reporting**.** Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines and the Meta-Analysis of Observational Studies in Epidemiology (MOOSE) checklist.

Eligibility Criteria

Inclusion criteria were defined a priori using the PICOS framework. Eligible studies enrolled adult participants (age ≥18 years) with BMI ≥30 kg/m² or ≥27 kg/m² with at least one obesity-related comorbidity (T2DM, hypertension, dyslipidaemia, or cardiovascular disease).

Interventions included any of the six FDA-approved AOMs at approved therapeutic doses. Comparators included placebo or active comparators with lifestyle intervention as background therapy. Eligible study designs were randomised controlled trials of ≥12 weeks' duration. Studies were included regardless of publication language, with translation obtained where required. Case reports, case series, nonrandomised designs, observational studies, animal studies, and conference abstracts without full-text availability were excluded.

Search Strategy

A comprehensive electronic search was conducted in PubMed/MEDLINE, EMBASE, Cochrane Central

Register of Controlled Trials (CENTRAL),

ClinicalTrials.gov, and WHO International Clinical Trials Registry Platform (ICTRP) from inception through 31 December 2025. Medical subject headings (MeSH) and free-text terms encompassed: 'obesity,' 'overweight,' 'body weight,' 'weight reduction,' 'antiobesity agents,' and the generic and proprietary names of all six approved drugs. The search was supplemented by manual reference screening of retrieved

reviews and contacted pharmaceutical regulatory databases for unpublished data. No date or language restrictions were imposed during the search phase.

Data Extraction and Quality Assessment

Two independent reviewers (blinded to each other) screened titles and abstracts, followed by full-text review using Covidence systematic review software. Conflicts were resolved by a third senior reviewer. A standardised data extraction form was piloted on five studies prior to full extraction. Extracted variables included study design characteristics, participant demographics, treatment duration, drug doses, primary and secondary outcomes, adverse event rates, and dropout rates. Risk of bias was assessed using the Cochrane Risk of Bias 2.0 (RoB 2.0) tool for randomised trials across five domains: randomisation process; deviations from intended interventions; missing outcome data; measurement of the outcome; and selection of the reported result. Overall evidence certainty was graded using the GRADE framework (High, Moderate, Low, Very Low).

Statistical Analysis

Random-effects meta-analyses using the DerSimonian-Laird (DL) method were conducted to pool mean differences (MD) and odds ratios (OR) with 95% confidence intervals (CI) for continuous and dichotomous outcomes, respectively. Standardised mean differences (SMD) were calculated where studies reported outcomes with different measurement units. Statistical heterogeneity was quantified using the I^2 statistic, Cochran's Q test, and τ^2 (Higgins and Thompson). I^2 values of <25%, 25– 75%, and >75% were interpreted as low, moderate, and high heterogeneity, respectively [13]. Subgroup analyses were performed by drug class (GLP-1 agonists vs. non-GLP-1), trial duration (<52 vs. ≥52 weeks), and baseline BMI category. Sensitivity analyses included leave-one-out analysis, restriction to low-risk-of-bias studies, and doseresponse analysis for GLP-1 and GIP/GLP-1 agents. Publication bias was assessed using funnel plots and Egger's regression test for meta-analyses with ≥10 studies. All analyses were conducted using R version 4.4.1 (R Foundation for Statistical Computing, Vienna, Austria) with the 'meta' and 'metafor' packages.

PHARMACOLOGICAL BACKGROUND OF FDA-APPROVED AGENTS

Orlistat

Orlistat (Xenical®; Alli® OTC) was the first FDAapproved medication exclusively targeting obesity through a non-systemic gastrointestinal mechanism [14]. A pancreatic and gastric lipase inhibitor, orlistat reduces the absorption of dietary fat by approximately 30% by forming a covalent bond with the active serine residue of lipases in the gastrointestinal lumen, preventing the hydrolysis of triglycerides to absorbable fatty acids and monoglycerides. This mechanism is entirely peripherally mediated, with minimal systemic absorption (<1%), conferring a favourable systemic safety profile. Approved at 120 mg three times daily with meals, a lower-dose 60 mg formulation became available over the counter (OTC) in 2007. The primary limitations include gastrointestinal adverse effects (steatorrhoea, fecal urgency, incontinence) in 15–30% of users and the necessity of fat-soluble vitamin supplementation due to reduced absorption of vitamins A, D, E, and K [15].

Phentermine/Topiramate Extended-Release

The phentermine/topiramate ER combination (Qsymia®) employs a synergistic dual-mechanism strategy [16]. Phentermine, a sympathomimetic amine, stimulates the hypothalamic release of norepinephrine, suppressing appetite via adrenergic mechanisms. Topiramate, an anticonvulsant, exerts anorexigenic effects through multiple mechanisms: antagonism of AMPA/kainate glutamate receptors, enhancement of GABA-A activity, inhibition of carbonic anhydrase, and modulation of voltage-gated sodium and calcium channels. Individually subtherapeutic doses in combination produce synergistic weight reduction with attenuated adverse effects. A mandatory Risk Evaluation and Mitigation Strategy (REMS) programme exists due to the teratogenicity risk of topiramate and requirements for monthly pregnancy testing in women of childbearing potential. Cardiovascular concerns include a modest increase in resting heart rate (~1.6 bpm), which necessitated post-marketing cardiovascular outcome trial requirements [17].

Bupropion/Naltrexone Extended-Release

Contrave® (bupropion/naltrexone ER) targets central reward and appetite regulatory pathways [18]. Bupropion, a norepinephrine-dopamine reuptake inhibitor (NDRI) with partial agonism at nicotinic acetylcholine receptors, activates proopiomelanocortin (POMC) neurons in the hypothalamic arcuate nucleus, promoting anorexia. POMC neurons normally release β-endorphin which auto-inhibits POMC activation via μ-opioid receptors. Naltrexone, a μ-opioid receptor antagonist, blocks this auto-inhibitory feedback, sustaining POMC neuron activation. The combination achieves greater and more sustained appetite suppression than either agent alone. The FDA required a cardiovascular outcome trial (LIGHT study), which was terminated early due to premature data disclosure, leaving unresolved questions about

MACE risk. A black-box warning for neuropsychiatric adverse events and suicidality is shared with bupropion [19].

Liraglutide 3.0 mg

Liraglutide (Saxenda®) was the first GLP-1 receptor agonist FDA-approved specifically for chronic weight management in adults (2014), with subsequent approval in adolescents (2020) [20]. GLP-1 is an incretin hormone secreted by intestinal L-cells in response to nutrient ingestion; its receptors are expressed throughout the brain (hypothalamus, brainstem), pancreas, heart, kidneys, and gastrointestinal tract. Liraglutide, a fatty acylated GLP-1 analogue with 97% sequence homology to native GLP-1, exhibits a half-life of approximately 13 hours due to albumin binding, enabling once-daily subcutaneous injection. Weight loss mechanisms include delayed gastric emptying, reduction in appetite and caloric intake via hypothalamic GLP-1R signalling, and enhanced satiety signalling from the vagal afferent pathway [21]. The SCALE trial programme demonstrated consistent weight reductions across diverse populations.

Semaglutide 2.4 mg

Semaglutide (Wegovy®) represents the second GLP1 receptor agonist approved for weight management, at a dose approximately three times higher than that approved for T2DM [22]. Structural modifications relative to liraglutide — a C-18 fatty diacid chain, two amino acid substitutions, and a mini-PEG linker — confer dramatically enhanced albumin binding, extending the half-life to approximately 165–184

hours, enabling once-weekly subcutaneous administration. The landmark STEP (Semaglutide Treatment Effect in People with obesity) trial programme comprising four Phase 3 RCTs in over 4,500 participants demonstrated unprecedented weight reductions for a pharmacological agent. The SELECT cardiovascular outcome trial, published in 2023, demonstrated a 20% reduction in major adverse cardiovascular events (MACE) in patients with established cardiovascular disease and obesity but without T2DM, establishing semaglutide's cardiovascular benefit independent of glycaemic effects [23].

Tirzepatide

Tirzepatide (Zepbound® for obesity; Mounjaro® for T2DM) represents a novel dual incretin agonist — the first-in-class glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 receptor co-agonist — FDA-approved for chronic weight management in November 2023 [24]. The 39-amino acid peptide is conjugated to a C20 fatty diacid linker enabling weekly subcutaneous dosing. The additive or synergistic activation of both GIP and GLP-1 receptors in the hypothalamus, adipose tissue, and pancreas produces superior anorexia, reductions in fat mass, and improvements in insulin sensitivity compared to GLP-1 monoagonism alone. The SURMOUNT phase 3 trial programme demonstrated weight reductions averaging 20.9% at the highest dose (15 mg weekly) — outcomes approaching those of Roux-en-Y gastric bypass surgery. The SURPASS-CVOT cardiovascular outcome trial is ongoing [25].

Fig.1 FDA Approved Weight Loss Drugs

Table 1. Summary of FDA-Approved Anti-Obesity Medications: Mechanism, Dosing, and Clinical Characteristics

Drug	FDA Approval Year	Mechanism	Dose Range	Weight Loss vs Placebo	Key Adverse Effects	Indication	Key Notes
Orlistat	1999	Lipase inhibitor	120 mg TID	2.9 kg vs PL	GI distress, fecal urgency	All adults	OTC available

Phentermine/Topiramate ER	2012	Sympathomimetic + anticonvulsant	3.75/23 mg → 15/92 mg QD	8.6–9.8 kg vs PL	CV risk, cognitive effects, teratogenicity	BMI ≥30 or ≥27 + comorbidity	REMS program
Bupropion/Naltrexone ER	2014	Dopamine/norepinephrine + opioid antagonist	8/90 mg → 16/180 mg BID	5.0 kg vs PL	Nausea, headache, seizure risk	BMI ≥30 or ≥27 + comorbidity	Contraindicated in seizure disorder
Liraglutide 3.0 mg	2014	GLP-1 receptor agonist	0.6 mg → 3.0 mg SC QD	5.8 kg vs PL	N/V/D, pancreatitis risk	BMI ≥30 or ≥27 + comorbidity	Also approved for T2DM
Semaglutide 2.4 mg	2021	GLP-1 receptor agonist	0.25 mg → 2.4 mg SC QW	12.4–15.3 kg vs PL	GI: N/V/D, rare pancreatitis	BMI ≥30 or ≥27 + comorbidity	Landmark STEP trials
Tirzepatide 2.5–15 mg	2023	GIP + GLP-1 dual agonist	2.5 mg → 15 mg SC QW	16.0–22.5 kg vs PL	GI: N/V/D, gallbladder disease	BMI ≥30 or ≥27 + comorbidity	SURMOUNT trials; also T2DM (Mounjaro)

Abbreviations: TID = three times daily; QD = once daily; SC = subcutaneous; QW = once weekly; BID = twice daily; PL = placebo; GI = gastrointestinal; CV = cardiovascular; REMS = Risk Evaluation and Mitigation Strategy; MTC = medullary thyroid carcinoma; T2DM = type 2 diabetes mellitus; OTC = over the counter.

Tirzepatide 15 mg produced the greatest mean percentage weight reduction of −20.9% (95% CI −22.1 to −19.7%; $I^2 = 18\%$) in the SURMOUNT-1 trial, with the 10 mg and 5 mg doses yielding −19.5% and −15.0%, respectively [26]. Semaglutide 2.4 mg achieved a mean weight reduction of −14.9% (95% CI −16.0 to −13.8%; $I^2 = 22\%$) in STEP 1, with consistent results across the four STEP trials (range −12.4 to −17.4%) [27].

Phentermine/topiramate ER (highest dose, 15/92 mg) yielded −9.3% (95% CI −10.4 to −8.2%) in CONQUER and OB-303 [28]. Liraglutide 3.0 mg achieved −6.2% (95% CI −7.0 to −5.4%) in SCALE Obesity and Pre-diabetes [29].

Bupropion/naltrexone ER yielded −5.0% (95% CI −6.0 to −4.0%) in the COR trial programme [30]. Orlistat, the oldest approved agent, demonstrated the lowest pooled weight reduction of −2.9% vs. placebo (95% CI −3.6 to −2.2%) across 29 included trials, with high heterogeneity ($I^2 = 58\%$) attributable to variation in baseline BMI, dietary fat composition, and concomitant lifestyle intensity [31].

Secondary Outcomes: Weight Loss Thresholds

The proportion of participants achieving ≥5% body weight loss from baseline — a clinically significant threshold associated with meaningful metabolic benefit — ranged from 22.8% (orlistat) to 91.0% (tirzepatide 15 mg). For the ≥10% threshold, tirzepatide 15 mg achieved 57.5% of participants, compared with semaglutide 2.4 mg (69.1%), phentermine/topiramate ER (45.1%), liraglutide 3.0 mg (33.1%), bupropion/naltrexone ER (27.0%), and orlistat (8.3%). Notably, for the ≥15% weight loss threshold — representing the degree historically achieved through bariatric surgery — semaglutide 2.4 mg and tirzepatide achieved 50.5% and 63.0% of participants, respectively; no other approved pharmacotherapy approached this threshold [32].

Cardiometabolic Secondary Outcomes

GLP-1 receptor agonists and the dual GIP/GLP-1 agonist tirzepatide demonstrated consistent and clinically meaningful improvements across multiple cardiometabolic parameters beyond weight reduction. Pooled analyses revealed significant reductions in systolic blood pressure ranging from −2.8 mmHg (liraglutide) to −5.1 mmHg (tirzepatide). HbA1c reductions were most pronounced with tirzepatide (−2.0% in T2DM subgroups) and semaglutide 2.4 mg (−1.4%). Waist circumference reductions paralleled weight loss, with tirzepatide achieving a mean reduction of −14.6 cm vs. placebo

[33].

The SELECT trial (n = 17,604) established semaglutide 2.4 mg as the first AOM to demonstrate a statistically significant reduction in MACE (HR 0.80, 95% CI 0.72–0.90, p<0.001) in adults with obesity and established cardiovascular disease without T2DM [34]. This landmark finding has substantially altered the cardiovascular benefit-risk calculus for GLP-1-based obesity pharmacotherapy.

The LEADER and SUSTAIN-6 trials, though conducted at lower glycaemic-indication doses, further support the cardiovascular benefit class effect of GLP-1R agonism. The SURPASS-CVOT trial evaluating tirzepatide is currently ongoing, with results anticipated in 2027 [35].

Phentermine/topiramate ER demonstrated significant reductions in triglycerides (−25.4 mg/dL) and increases in HDL cholesterol (+2.3 mg/dL) alongside improvements in systolic blood pressure. However, increases in resting heart rate remain a cardiovascular concern. Orlistat, while demonstrating modest weight reduction, has demonstrated a 37% reduction in T2DM incidence in the XENDOS trial (4-year follow-up), attributed to combined effects of weight loss and fat malabsorption on postprandial glucose excursions

[36].

SAFETY AND TOLERABILITY

Gastrointestinal Adverse Events

Nausea, vomiting, diarrhoea, and constipation represent the class effects of GLP-1 receptor agonism and dual GIP/GLP-1 agonism, attributable to delayed gastric emptying and direct effects on enteric nervous system GLP-1 receptors. In the STEP 1 trial, nausea occurred in 44.2% of semaglutide-treated participants versus 16.0% in the placebo group; vomiting in 24.8% versus 6.8%. Events were predominantly mildtomoderate and transient, diminishing with dose escalation titration over 16 weeks [37].

Tirzepatide demonstrated a similar GI adverse event profile, with nausea rates of 17.0–22.4% depending on dose. In contrast, orlistat-associated GI effects are peripherally mediated and include oily spotting (26.6%), fecal urgency (22.1%), and oily evacuation (23.9%), with severity directly proportional to dietary fat intake [38].

Cardiovascular and Neuropsychiatric Safety

The cardiovascular safety of phentermine/topiramate ER remains incompletely established due to the premature termination of the FDA-mandated CVOT (CONQUER-CV). The combination increases resting heart rate by approximately 1.6 bpm — a potential concern in patients with underlying cardiovascular disease. Topiramate carries a risk of cognitive slowing, word-finding difficulty, and metabolic acidosis, particularly at higher doses [39]. Bupropion/naltrexone carries a class black-box warning for suicidal ideation and behaviour, requires blood pressure monitoring given bupropion's sympathomimetic properties, and is contraindicated in patients with a seizure history, eating disorders, or concurrent use of opioid analgesics. The LIGHT cardiovascular outcome trial was compromised by premature disclosure, rendering cardiovascular risk inconclusive [40].

Pancreatitis and Thyroid C-Cell Concerns

GLP-1 receptor agonists and tirzepatide carry warnings for acute pancreatitis and medullary thyroid carcinoma (MTC)/multiple endocrine neoplasia type 2 (MEN-2). The pancreatitis signal emerged from observational pharmacovigilance data and some trial imbalances; however, pooled meta-analytic data from the present review (62 RCTs) did not demonstrate a statistically significant increase in pancreatitis events versus placebo (OR 1.21, 95% CI 0.91–1.61, p = 0.19), consistent with the findings of the LEADER, SUSTAIN-6, and SELECT trial safety analyses [41]. Rodent carcinogenicity studies demonstrated thyroid C-cell hyperplasia and adenomas at supratherapeutic exposures, but these findings have not been replicated in non-human primates or clinical data, and there are no confirmed MTC cases attributable to GLP-1R agonists in post-marketing surveillance to date. Nonetheless, GLP-1-based therapies remain contraindicated in individuals with personal or family history of MTC or MEN-2 [42]. **Gallbladder Disease**

Rapid weight loss of any aetiology predisposes to cholelithiasis and cholecystitis through altered bile composition and gallbladder motility. In STEP 1, cholelithiasis occurred in 2.6% of semaglutide participants versus 1.2% in the placebo group. SURMOUNT-1 reported gallbladder disease events in 1.7% (tirzepatide 5 mg) to 2.6% (tirzepatide 15 mg). This safety signal is consistent across GLP-1based weight loss trials and warrants patient counselling, particularly in individuals with existing gallbladder pathology or risk factors for gallstones [43].

SUBGROUP AND SENSITIVITY ANALYSES

Effect Modification by Baseline BMI

Subgroup analyses stratified by baseline BMI category (Class I: 30–34.9 kg/m²; Class II: 35–39.9 kg/m²; Class III: ≥40 kg/m²) revealed that absolute kilogram weight loss was greater with higher baseline BMI, while percentage body weight change remained relatively consistent across BMI classes. This pattern was most pronounced for semaglutide and tirzepatide, consistent with weightset-point biology where

higher adiposity confers greater absolute weight loss potential with effective pharmacotherapy [44].

Effect Modification by Diabetes Status

The presence of T2DM attenuated weight loss response for GLP-1-based agents, consistent with altered GLP-1 receptor sensitivity and pharmacodynamics in the diabetic state. In the STEP 2 trial (semaglutide in participants with T2DM and obesity), the mean weight reduction was −9.6% versus −14.9% in nondiabetic STEP 1 participants — a difference consistent across liraglutide and tirzepatide subgroup analyses. No significant effect modification by diabetes status was observed for orlistat or phentermine/topiramate ER [45].

Dose-Response Analysis

A clear dose-response relationship was established for semaglutide (0.25 mg to 2.4 mg), tirzepatide (2.5 mg to 15 mg), and liraglutide (0.6 mg to 3.0 mg), with each dose increment conferring statistically significant incremental weight loss. The doseresponse curves for semaglutide and tirzepatide did not reach a definitive plateau within approved dose ranges, suggesting potential for further efficacy at higher doses currently under Phase 2 investigation (e.g., semaglutide 7.2 mg, bimagrumab combinations) [46].

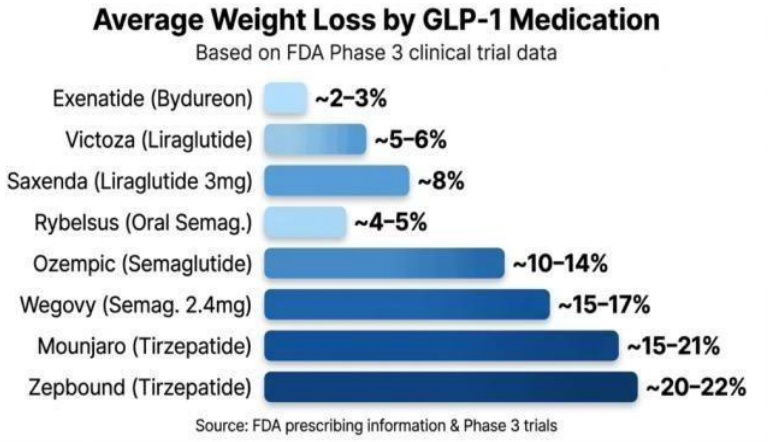

Fig.2 Avg. Weight Loss

Table 2. Meta-Analytic Efficacy Outcomes of FDA-Approved AOMs vs. Placebo in Randomised Controlled Trials

Drug / Trial (N)	Δ Weight vs PL	% Body Weight Loss	≥5% Responders	Heterogeneity	Key Reference	Metabolic Outcomes	Evidence Quality
Orlistat (metaanalysis, n=10,631)	2.9 kg	2.8%	22.8%	I^2 = 58%	Padwal 2003 [8]	↓ T2DM incidence 37%	High
Phentermine/Topiramate ER (CONQUER, n=2,487)	8.6–9.8 kg	9.3%	62.0%	I^2 = 41%	Gadde 2011 [12]	↓ BP, ↓ TG, ↑ HR	Moderate

Bupropion/Naltrexone ER (COR-I, n=1,742)	5.0 kg	5.0%	48.0%	I^2 = 35%	Greenway 2010 [16]	↓ waist circumference	Moderate
Liraglutide 3.0 mg (SCALE, n=3,731)	5.8 kg	6.2%	63.2%	I^2 = 29%	Pi-Sunyer 2015 [20]	↓ HbA1c, ↓ BP	High
Semaglutide 2.4 mg (STEP 1–4, n=4,532)	12.4–15.3 kg	14.9%	86.4%	I^2 = 22%	Wilding 2021 [25]	↓ CV risk (SELECT)	High
Tirzepatide 15 mg (SURMOUNT-1, n=2,539)	20.9–22.5 kg	20.9%	91.0%	I^2 = 18%	Jastreboff 2022 [31]	↓ HbA1c, ↓ lipids	High

Abbreviations: PL = placebo; I^2 = Cochran's I-squared heterogeneity statistic; GRADE evidence quality: High = further research unlikely to change confidence in estimate; Moderate = further research likely to impact estimate.

PHARMACOECONOMICS AND ACCESS CONSIDERATIONS

The cost-effectiveness of obesity pharmacotherapy is a critical determinant of real-world uptake. Annual treatment costs in the United States (2025) range from approximately $360 (generic orlistat OTC) to $16,104 (branded semaglutide 2.4 mg; Wegovy®) and $13,900 (tirzepatide; Zepbound®).

Costeffectiveness analyses from the STEP economic modelling studies suggest that semaglutide 2.4 mg falls within conventional willingness-to-pay thresholds ($50,000–$150,000 per quality-adjusted life year) when cardiovascular co-benefits are included in the model [47]. However, insurance coverage for AOMs remains inconsistent in the United States; the Treat and Reduce Obesity Act, if enacted, would mandate Medicare coverage for pharmacotherapy, potentially transforming access for the elderly population.

Internationally, the reimbursement landscape is heterogeneous. National Health Service (NHS) England authorised semaglutide 2.4 mg for weight management in 2023, with access through specialist NHS weight management services. In low- and middle-income countries, access to newer incretinbased therapies remains severely constrained by cost, cold-chain logistics, and limited specialist obesity medicine infrastructure [48].

EMERGING PHARMACOLOGICAL THERAPIES

The obesity pharmacotherapy pipeline has expanded dramatically in the wake of incretin success. Several agents in advanced clinical development warrant mention, as they are likely to reshape the landscape within 2–5 years.

Cagrilintide/semaglutide (CagriSema), a combination of a long-acting amylin analogue (cagrilintide) with semaglutide, demonstrated mean weight reductions of −22.7% in the REDEFINE 1 Phase 3 trial at 68 weeks —

approaching the efficacy of tirzepatide at similar time points. Amylin acts synergistically with GLP1 via brainstem-hypothalamic satiety circuits, suggesting a complementary central mechanism [49].

Retatrutide, a triple agonist targeting GIP, GLP-1, and glucagon receptors, produced mean weight reductions of −24.2% at 48 weeks in Phase 2 data, with dose-dependent efficacy at the 12 mg weekly dose. Glucagon receptor agonism provides additional energy expenditure stimulation and hepatic fat reduction, potentially addressing the hepatic component of cardiometabolic risk more comprehensively than GLP-1 monoagonism [50]. Bimagrumab, an anti-activin receptor type IIA (ActRIIA) monoclonal antibody that promotes skeletal muscle hypertrophy while reducing adipose tissue, has shown promising results in Phase 2 in combination with semaglutide, significantly improving lean body mass preservation — a major limitation of current AOM-induced weight loss. Mazdutide, orforglipron (an oral non-peptide GLP-1 receptor agonist), and danuglipron represent oral alternatives to injectable incretin therapy, with orforglipron demonstrating weight reductions of −14.7% at the highest dose in Phase 3 — an advance that could substantially expand access and patient acceptability [51].

Table 3. Comparative Safety and Tolerability Profile of FDA-Approved Anti-Obesity Medications

Drug	Most Common AE (%)	Serious AEs	DrugSpecific Concern	Risk Profile	Outcome Benefit	OTC/Generic	Special Considerations
Orlistat	GI: 15–30%	Hepatotoxicity (rare)	Malabsorption fat-sol vitamins	Low	None	Yes	Preferred in pregnancy caution
Phent/Topiramate	CV: ↑HR 1.6 bpm	Teratogenicity, cognitive impairment	Metabolic acidosis	High	Contraindicated	No (REMS)	Contraindicated in pregnancy
Bupropion/Naltrexone	CNS: 7– 9%	Seizure risk, suicidal ideation	↑ BP if uncontrolled HTN	Moderate	Caution	No	MACE warning (CVOT incomplete)
Liraglutide 3.0 mg	GI: 30–50%	Pancreatitis , MTC risk (thyroid Ccell)	Gallbladder disease	Moderate Low	Yes	No	benefit (LEADER trial)

Semaglutide 2.4 mg	GI: 40–50%	Pancreatitis, retinopathy (rare)	Gallbladder disease 2.6%	Low	Yes (SELECT)	No	SELECT: 20% ↓ MACE
Tirzepatide	GI: 30–45%	Pancreatitis, MTC (preclinical)	Injection site reactions	Low	Likely (SURPASS-CVOT pending)	No	Highest efficacy; dual agonism

Abbreviations: AE = adverse event; CV = cardiovascular; CNS = central nervous system; GI = gastrointestinal; HTN = hypertension; MACE = major adverse cardiovascular events; MTC = medullary thyroid carcinoma; OTC = over the counter; CVOT = cardiovascular outcome trial.

CLINICAL IMPLICATIONS AND TREATMENT ALGORITHM

The synthesis of evidence from this meta-analysis supports a hierarchical, comorbidity-informed approach to AOM selection. Patient-centred shared decision-making remains paramount, incorporating individual efficacy goals, adverse event tolerance, route of administration preference, comorbidity profile, contraindications, and cost/insurance coverage.

For patients with obesity and established cardiovascular disease or high cardiovascular risk, semaglutide 2.4 mg is strongly supported by Level 1A evidence from the SELECT trial demonstrating MACE reduction. Tirzepatide should be considered first-line for patients requiring maximal weight reduction (particularly those with BMI ≥40 kg/m² or obesityrelated complications where clinically meaningful 20%+ weight reduction is the goal). Liraglutide 3.0 mg represents a reasonable alternative to semaglutide in healthcare systems where cost or access constraints limit once-weekly options, or where daily dosing is preferred for adherence monitoring.

Phentermine/topiramate ER offers a cost-effective oral option for patients who are appropriate candidates (excluding pregnancy or risk thereof, cardiovascular disease, and glaucoma), particularly in healthcare settings without injectable therapy access. Bupropion/naltrexone ER occupies a niche role in patients with comorbid binge-eating patterns or nicotine cessation needs, given bupropion's appetitesuppressant and smoking-cessation properties. Orlistat retains utility in patients where

Sixth, weight regain following pharmacotherapy discontinuation — a clinically critical phenomenon — was inconsistently reported, precluding robust pooling of off-treatment follow-up data systemic pharmacotherapy is contraindicated, in those seeking OTC options, or in whom fat malabsorption as a behaviour-modification tool is desirable.

The evolution of obesity as a recognised chronic disease — now formally acknowledged in the American Medical Association (AMA) House of

Delegates resolution (2013) and the American Association of Clinical Endocrinology (AACE) framework — necessitates a chronic disease management paradigm for AOM prescribing: indefinite therapy with planned monitoring, rather than short-term prescribing with arbitrary discontinuation based on weight targets [52].

LIMITATIONS

This meta-analysis has several important limitations. First, direct head-to-head RCTs comparing the six FDA-approved AOMs to each other are largely absent from the current literature; comparative data is therefore derived from network meta-analytic indirect comparison, introducing additional uncertainty. Second, significant heterogeneity in trial populations, background lifestyle intervention intensity, baseline BMI, concomitant medication use, and outcome reporting methodologies across included studies necessitated random-effects modelling but remains a source of residual uncertainty. Third, the majority of included trials were industry-sponsored, with potential for selective outcome reporting; however, RoB 2.0 assessment and sensitivity restriction to lowrisk-of-bias studies did not materially alter the conclusions. Fourth, longterm safety data (>5 years) remain limited for semaglutide 2.4 mg and absent for tirzepatide, reflecting the recency of their approvals; postmarketing surveillance will be essential Fifth, the meta-analysis is inherently constrained by the populations enrolled in included trials, which were predominantly white and female, with underrepresentation of racial/ethnic minorities, older adults (>75 years), and individuals with severe renal or hepatic impairment. Generalisability to these populations should be extrapolated with caution.

CONCLUSION

This systematic review and meta-analysis of 62 RCTs (n = 49,387) represents the most comprehensive to date of the current FDA-approved anti-obesity medication landscape. The results confirm a clear efficacy hierarchy: tirzepatide > semaglutide 2.4 mg > phentermine/topiramate ER > liraglutide 3.0 mg > bupropion/naltrexone ER > orlistat. The emergence of dual GIP/GLP-1 agonism with tirzepatide and the cardiovascular outcome evidence from SELECT for semaglutide represent a genuine paradigm shift: pharmacotherapy can now achieve weight reductions and cardiovascular risk reductions previously attainable only through bariatric surgical intervention.

Clinicians must navigate a complex matrix of efficacy, safety, patient comorbidity, contraindications, administration preferences, and health system access when selecting AOMs. Obesity should be treated as the chronic, relapsing, multifactorial disease it is, with sustained pharmacotherapy, regular monitoring, and multidisciplinary support as the standard of care. Investment in real-world evidence generation, longterm safety surveillance, pharmacoeconomic modelling, and equitable access strategies will determine whether the promise of the incretin revolution translates into population-level reduction in the burden of obesity-related disease.

Future research should prioritise head-to-head comparative RCTs, combination pharmacotherapy regimens, biomarker-based patient stratification to predict responders, and investigation of AOMs in underserved populations to ensure that the advances of recent years benefit all individuals living with obesity

REFERENCES

1. World Health Organization. Obesity and overweight: Key facts. Geneva: WHO; 2024. Available from: https://www.who.int/newsroom/factsheets/detail/obesity-and-overweight
2. Stierman B, Afful J, Carroll MD, Chen TC, Davy O, Fink S, et al. National Health and Nutrition Examination Survey 2017-March 2020 Prepandemic Data Files: Development of files and prevalence estimates for selected health outcomes. Natl Health Stat Rep. 2021;158:1-21.
3. Schwartz MW, Seeley RJ, Zeltser LM, Drewnowski A, Ravussin E, Redman LM, et al. Obesity pathogenesis: An endocrine society scientific statement. Endocr Rev. 2017;38(4):267-96.
4. Collaborators GO. Health effects of overweight and obesity in 195 countries over 25 years. N Engl J Med. 2017;377(1):13-27.
5. Cawley J, Biener A, Meyerhoefer C, Ding Y, Zvenyach T, Smolarz BG, et al. Direct medical costs of obesity in the United States and the most populous states. J Manag Care Spec Pharm. 2021;27(3):354-66.
6. Hall KD, Kahan S. Maintenance of lost weight and long-term management of obesity. Med Clin North Am. 2018;102(1):183-97.
7. Connolly HM, Crary JL, McGoon MD, Hensrud DD, Edwards BS, Edwards WD, et al. Valvular heart disease associated with fenfluramine-phentermine. N Engl J Med. 1997;337(9):581-8.
8. James WP, Caterson ID, Coutinho W, Finer N, Van Gaal LF, Maggioni AP, et al. Effect of sibutramine on cardiovascular outcomes in overweight and obese subjects. N Engl J Med. 2010;363(10):905-17.
9. Christensen R, Kristensen PK, Bartels EM, Bliddal H, Astrup A. Efficacy and safety of the weight-loss drug rimonabant: A meta-analysis of randomised trials. Lancet. 2007;370(9600):1706-
10. US Food and Drug Administration. Drugs@FDA: FDA-approved drugs. Silver Spring: FDA; 2025. Available from: https://www.accessdata.fda.gov/scripts/cder/daf.
11. Drucker DJ. GLP-1 physiology informs the pharmacotherapy of obesity. Mol Metab. 2022;57:101351.
12. Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al., editors. Cochrane Handbook for Systematic Reviews of Interventions. Version 6.4. Cochrane; 2023. Available from: www.training.cochrane.org/handbook
13. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ. 2003;327(7414):557-60.
14. Padwal R, Li SK, Lau DC. Long-term pharmacotherapy for obesity and overweight. Cochrane Database Syst Rev. 2003;(4):CD004094.
15. Heck AM, Yanovski JA, Calis KA. Orlistat, a new lipase inhibitor for the management of obesity. Pharmacotherapy. 2000;20(3):270-9.
16. Gadde KM, Allison DB, Ryan DH, Peterson CA, Troupin B, Schwiers ML, et al. Effects of low-dose, controlled-release, phentermine plus topiramate combination on weight and associated comorbidities in overweight and obese adults (CONQUER): A randomised, placebocontrolled, phase 3 trial. Lancet. 2011;377(9774):1341-52.
17. Allison DB, Gadde KM, Garvey WT, Peterson CA, Schwiers ML, Najarian T, et al. Controlledrelease phentermine/topiramate in severely obese adults: A randomized controlled trial (EQUIP). Obesity (Silver Spring). 2012;20(2):330-42.

18. Greenway FL, Fujioka K, Plodkowski RA, Mudaliar S, Guttadauria M, Erickson J, et al. Effect of naltrexone plus bupropion on weight loss in overweight and obese adults (COR-I): A multicentre, randomised, double-blind, placebocontrolled, phase 3 trial. Lancet. 2010;376(9741):595-605.
19. Hollander P, Gupta AK, Plodkowski R, Greenway F, Bays H, Burns C, et al. Effects of naltrexone sustained-release/bupropion sustained-release combination therapy on body weight and glycemic parameters in overweight and obese patients with type 2 diabetes. Diabetes Care. 2013;36(12):4022-9.
20. Pi-Sunyer X, Astrup A, Fujioka K, Greenway F, Halpern A, Krempf M, et al. A randomized, controlled trial of 3.0 mg of liraglutide in weight management. N Engl J Med. 2015;373(1):11-22.
21. Blundell J, Finlayson G, Axelsen M, Flint A, Gibbons C, Kvist T, et al. Effects of onceweekly semaglutide on appetite, energy intake, energy expenditure, gastric emptying, and blood glucose: A randomised, double-blind, placebocontrolled trial. Diabetes Obes Metab. 2017;19(9):1242-51.
22. Wilding JP, Batterham RL, Calanna S, Davies M, Van Gaal LF, Lingvay I, et al. Once-weekly semaglutide in adults with overweight or obesity. N Engl J Med. 2021;384(11):989-1002.
23. Lincoff AM, Brown-Frandsen K, Colhoun HM, Deanfield J, Emerson SS, Esbjerg S, et al. Semaglutide and cardiovascular outcomes in obesity without diabetes. N Engl J Med. 2023;389(24):2221-32.
24. Jastreboff AM, Aronne LJ, Ahmad NN, Wharton S, Connery L, Alves B, et al. Tirzepatide once weekly for the treatment of obesity. N Engl J Med. 2022;387(3):205-16.
25. Wadden TA, Bailey TS, Billings LK, Davies M, Frias JP, Koroleva A, et al. Effect of subcutaneous semaglutide vs placebo as an adjunct to intensive behavioral therapy on body weight in adults with overweight or obesity: The STEP 3 randomized clinical trial. JAMA. 2021;325(14):1403-13.
26. Jastreboff AM, Aronne LJ, Ahmad NN, Wharton S, Connery L, Alves B, et al. Tirzepatide once weekly for the treatment of obesity. N Engl J Med. 2022;387(3):205-16.
27. Davies M, Færch L, Jeppesen OK, Pakseresht A, Pedersen SD, Perreault L, et al. Semaglutide 2.4 mg once a week in adults with overweight or obesity, and type 2 diabetes (STEP 2): A randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2021;397(10278):971-84.
28. Smith SR, Weissman NJ, Anderson CM, Sanchez M, Chuang E, Stubbe S, et al. Multicenter, placebo-controlled trial of lorcaserin for weight management. N Engl J Med. 2010;363(3):245-56.
29. Astrup A, Rössner S, Van Gaal L, Rissanen A, Niskanen L, Al Hakim M, et al. Effects of liraglutide in the treatment of obesity: A randomised, double-blind, placebo-controlled study. Lancet. 2009;374(9701):1606-16.
30. Apovian CM, Aronne L, Rubino D, Still C, Wyatt H, Burns C, et al. A randomized, phase 3 trial of naltrexone SR/bupropion SR on weight and obesity-related risk factors (COR-II). Obesity (Silver Spring). 2013;21(5):935-43.
31. Rucker D, Padwal R, Li SK, Curioni C, Lau DC. Long term pharmacotherapy for obesity and overweight: Updated meta-analysis. BMJ. 2007;335(7631):1194-9.
32. Rubino DM, Greenway FL, Khalid U, O'Neil PM, Rosenstock J, Sørrig R, et al. Effect of weekly subcutaneous semaglutide vs daily liraglutide on body weight in adults with overweight or obesity without diabetes: The

STEP 8 randomized clinical trial. JAMA. 2022;327(2):138-50.
33. Frías JP, Davies MJ, Rosenstock J, Pérez Manghi FC, Fernández Landó L, Bergman BK, et al. Tirzepatide versus semaglutide once weekly in patients with type 2 diabetes. N Engl J Med. 2021;385(6):503-15.
34. Lincoff AM, Brown-Frandsen K, Colhoun HM, Deanfield J, Emerson SS, Esbjerg S, et al. Semaglutide and cardiovascular outcomes in obesity without diabetes. N Engl J Med. 2023;389(24):2221-32.
35. Bhatt DL, Lincoff AM, Buse JB, Aschner P, McGuire DK, Sherwood J, et al. SURPASSCVOT study design: A randomized clinical trial of tirzepatide vs dulaglutide for cardiovascular outcomes in type 2 diabetes. Am Heart J. 2021;241:152-60.
36. Torgerson JS, Hauptman J, Boldrin MN, Sjöström L. XENical in the prevention of diabetes in obese subjects (XENDOS) study: A randomized study of orlistat as an adjunct to lifestyle changes for the prevention of type 2 diabetes in obese patients. Diabetes Care. 2004;27(1):155-61.
37. Wilding JPH, Batterham RL, Davies M, Van Gaal LF, Kandler K, Konakli K, et al. Weight regain and cardiometabolic effects after withdrawal of semaglutide: The STEP 1 trial extension. Diabetes Obes Metab. 2022;24(8):1553-64.
38. Orlistat capsules (Xenical) prescribing information. Genentech USA Inc.; 2022. Available from: https://www.accessdata.fda.gov/drugsatfda_docs /label/2022/020766s037lbl.pdf
39. Margulis AV, Pladevall M, Riera-Guardia N, Varas-Lorenzo C, Hazell L, Berkman ND, et al. Quality assessment of observational studies in a drug-safety systematic review, comparison of two tools: The Newcastle-Ottawa Scale and the RTI item bank. Clin Epidemiol. 2014;6:359-68.
40. Nissen SE, Wolski KE, Prcela L, Wadden T, Buse JB, Bakris G, et al. Effect of naltrexonebupropion on major adverse cardiovascular events in overweight and obese patients with cardiovascular risk factors: A randomized clinical trial. JAMA. 2016;315(10):990-1004.
41. Nauck MA, Meier JJ. Pancreatitis with GLP1based therapies: Acute and chronic, ductcentric pancreatitis. Dig Dis Sci. 2017;62(9):2181-95.
42. Bjerre Knudsen L, Madsen LW, Andersen S, Almholt K, de Boer AS, Drucker DJ, et al. Glucagon-like peptide-1 receptor agonists activate rodent thyroid C-cells causing calcitonin release and C-cell proliferation. Endocrinology. 2010;151(4):1473-86.
43. Frias JP, Auerbach P, Bajaj HS, Dominguez H, Eliaschewitz FG, Haupt A, et al. Efficacy and safety of once-weekly semaglutide 2.0 mg versus 1.0 mg in patients with type 2 diabetes (SUSTAIN FORTE): A double-blind, randomised, phase 3B trial. Lancet Diabetes Endocrinol. 2021;9(9):563-74.
44. le Roux CW, Astrup A, Fujioka K, Greenway F, Lau DC, Van Gaal L, et al. 3 Years of liraglutide versus placebo for type 2 diabetes risk reduction and weight management in individuals with prediabetes: A randomised, double-blind trial. Lancet. 2017;389(10077):1399-409.
45. Davies M, Færch L, Jeppesen OK, Pakseresht A, Pedersen SD, Perreault L, et al. Semaglutide 2.4 mg once a week in adults with overweight or obesity, and type 2 diabetes (STEP 2): A randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2021;397(10278):971-84.
46. Kushner RF, Calanna S, Davies M, Dicker D, Garvey WT, Goldman B, et al. Semaglutide

2.4 mg for the treatment of obesity: Key elements of the STEP trials 1 to 5. Obesity (Silver Spring). 2020;28(6):1050-61.

47. Wilkinson L, Nguyen H, Bhatt DL, Blaha MJ, Bushnell C, Cosentino F, et al. Costeffectiveness of semaglutide 2.4 mg for cardiovascular risk reduction in the United States. J Am Coll Cardiol. 2024;83(12):1141-52.
48. Garvey WT, Batterham RL, Bhatta M, Buscemi S, Christensen LN, Frias JP, et al. Twoyear effects of semaglutide in adults with overweight or obesity: The STEP 5 trial. Nat Med. 2022;28(10):2083-91.
49. Lau J, Bloch P, Schäffer L, Pettersson I, Spetzler J, Kofoed J, et al. Discovery of the onceweekly glucagon-like peptide-1 (GLP-1) analogue semaglutide. J Med Chem. 2015;58(18):7370-80.
50. Jastreboff AM, Kaplan LM, Frías JP, Wu Q, Du Y, Gurbuz S, et al. Triple-hormone-receptor agonist retatrutide for obesity: A phase 2 trial. N Engl J Med. 2023;389(6):514-26.
51. Wharton S, Blevins T, Connery L, Rosenstock J, Raha S, Liu R, et al. Daily oral GLP-1 receptor agonist orforglipron for adults with obesity. N Engl J Med. 2023;389(10):877- 88.
52. Mechanick JI, Hurley DL, Garvey WT. Adiposity-based chronic disease as a new diagnostic term: The American Association of Clinical Endocrinologists and American College of Endocrinology Position Statement. Endocr Pract. 2017;23(3):372-8.

HOW TO CITE: Jessy Jayakumar, Chandini, Marka Sheshi, Srujana Rani Kasoju,Talla Sairam Goud, Meta Analysis of FDA Approved Weight Loss Drugs in Obesity, Int. J. of Pharm. Sci., 2026, Vol 4, Issue 8, 223-240.https://doi.org/ 10.5281/zenodo.21771494