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The Evolution of Medications for Obesity Management

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ABSTRACT

This narrative review provides an overview of progress in the development of obesity medications, including a synthesis of data describing the efficacy and safety of currently available agents and emerging therapeutic options. Historically, many obesity medications have been withdrawn from the market due to safety concerns. However, expansion in scientific knowledge of the mechanisms regulating appetite and energy balance has led to the development of medications with greater safety and efficacy. The current generation of injectable incretin analogs, semaglutide and tirzepatide, is associated with mean weight loss in the range of 15%–20% over approximately 12–18 months. These agents confer additional substantial cardiometabolic benefits, including reductions in adverse cardiovascular and kidney outcomes, and improvements in glycaemia, blood pressure, lipid profile and steatohepatitis. As therapeutic options continue to expand, obesity medications are poised to play a critical role in the management of cardiometabolic disease.

1 | Introduction

Obesity is defined by the World Health Organization as a body mass index of 30 kg/m^2 or greater, and characterized by accumulation of excess adipose tissue that presents a risk to health [1]. It was estimated that in 2022, 43% of adults were overweight, and 16% were living with obesity, with rates of obesity doubling since 1990 [1, 2]. Obesity is a key driver of numerous non-communicable diseases, including cardiovascular disease (CVD), type 2 diabetes (T2D), and several malignancies [3]. Importantly, effective management of obesity has extensive benefits on health. Therapeutic tools include lifestyle/behavioral interventions, obesity medications (OMs), endoscopic procedures, and metabolic bariatric surgery (MBS), with treatment strategies personalized to individual needs and goals of care [4]. OMs have been in use for more than a century, but many older medications were limited by insufficient safety, efficacy, or overall benefit for health and quality of life. Recent years have seen rapid developments in OMs, driven by a greater understanding of the physiology of appetite regulation. This narrative review article aims to briefly explore the history of OMs and provide an overview of current and emerging agents.

2 | Methods

A literature search of the PubMed database was conducted for articles published before November 2025, with search terms including obesity medications and specific names of pharmacologic agents currently or previously used or under development for obesity. An additional search was performed in August 2026. Where available, clinical guidelines, Phase 3 randomized controlled trials, systematic reviews, and meta-analyses were

preferentially included. Reference lists of included articles were reviewed for additional relevant studies.

3 | OMs Since the 20th Century

Historically, the landscape of obesity therapeutics was strewn with medications that were marketed but subsequently discontinued due to safety concerns [4]. As early as 1892, the use of thyroid hormone as a treatment for obesity emerged, on the basis of increasing metabolism but ultimately, this was not a successful therapeutic strategy due to the adverse consequences of hyperthyroidism [5]. 2,4-dinitrophenol (DNP) aimed to increase energy expenditure via mitochondrial uncoupling, [6] but had a high rate of adverse effects, including hyperthermia, diaphoresis, tachycardia, and tachypnoea [7]. The use of amphetamine in the 1930s produced weight loss, mainly through appetite suppression, and other sympathomimetics such as phentermine, benzphetamine, diethylpropion, and phendimetrazine were marketed, but all raised concern about their adverse effect profiles, potential for abuse and/or cardiovascular risk [8, 9]. However, phentermine and diethylpropion remain approved for short-term use in some regions. "Rainbow pills," which contained various combinations of amphetamines, thyroid hormones, laxatives, and diuretics, were heavily marketed in the mid-20th century, but were associated with many reported complications, including death [10]. Orlistat is a reversible inhibitor of gastrointestinal lipase, which reduces intestinal triglyceride absorption by around 30% when taken with meals [11]. As it is not systemically absorbed, it does not have the systemic adverse effects associated with earlier centrally-acting agents. However, its gastrointestinal side effects, primarily related to excess fat excretion (steatorrhea, fecal urgency, and oily leakage), limit its tolerability [12].

3.1 | Second Generation OMs

Identification of the adipocyte hormone leptin in 1994 [13] led to research that uncovered key neuroendocrine pathways that regulate appetite and body weight including the leptin-melanocortin pathway. During energy balance, leptin is released in proportion to fat mass, and acts via its receptor (leptin receptor) as a signal of the adequacy of fat stores to first-order neurons in the arcuate nucleus (ARC) of the hypothalamus. Leptin activates pro-opiomelanocortin (POMC) neurons and inhibits agouti-related protein/neuropeptide Y neurons in the ARC [14]. These neurons project to second-order neurons in other hypothalamic regions including the paraventricular nucleus, where POMC-derived peptide alpha-melanocyte stimulating hormone acts via the melanocortin 4 receptor (MC4R) to decrease food intake and increase energy expenditure via efferent outputs [14].

Hindbrain regions, including the nucleus of the solitary tract (NTS) and area postrema, have bidirectional connections with hypothalamic areas involved in energy homeostasis, and receive input from gut hormones responsive to nutrient ingestion, such as glucagon-like peptide-1 (GLP-1), peptide YY (PYY), and ghrelin. Integration of these inputs of short- and long-term energy status leads to coordinated modulation of appetite and energy expenditure. Moreover, appetite and food intake are strongly influenced by the rewarding properties of food, via connections between homeostatic pathways and mesolimbic reward circuits based in the ventral tegmental area and nucleus accumbens. Greater understanding of this complex circuitry led to new targets and approaches for obesity drug development [4].

Unlike phentermine, which has approval only for short-term use, the combination of phentermine with topiramate was approved for chronic weight management by the US Food and Drug Administration (FDA) in 2012. The specific mechanisms by which topiramate reduces appetite and body weight remain unknown, but it has multiple actions, including inhibition of carbonic anhydrase and glutamate activity, alongside increasing gamma-aminobutyric acid (GABA) activity and blocking voltage-gated sodium channels [15]. Common adverse effects of this combination therapy include insomnia, dizziness, paraesthesia, dry mouth, and altered taste sensation [16].

The combination of bupropion and naltrexone was rationally designed and developed as an obesity therapeutic based on the stimulating actions of bupropion, a reuptake inhibitor of noradrenaline and dopamine, on POMC neurons, with blockade of beta-endorphin mediated inhibitory feedback of these neurons by the opioid antagonist, naltrexone [17]. Naltrexone-bupropion received FDA approval for obesity management in 2014 [18]. Side effects, including headache, constipation, dry mouth, nausea, vomiting and dizziness, led to relatively high rates of attrition in clinical trials (40%–50% at 1 year) [19].

The peptide hormone GLP-1 is primarily produced by enteroendocrine L-cells in the distal intestine in response to intake of nutrients, particularly carbohydrates. GLP-1 is also synthesized in neurons of the NTS. It has numerous peripheral and central actions, including stimulation of insulin release from pancreatic beta-cells, suppression of glucagon secretion, slowing gastrointestinal motility, promotion of satiety and decreasing food reward. These actions result in improved glucose homeostasis and reduced food intake and body weight, making it attractive as a therapeutic target for obesity as well as T2D [20].

Liraglutide was the first GLP-1 receptor agonist (GLP-1RA) developed for management of obesity and was approved by the FDA in 2014. While endogenous GLP-1 has a half-life of only 1–2 min due to inactivation by the enzyme dipeptidylpeptidase-4 (DPP-4) [18], liraglutide is a synthetic GLP-1 analog with structural modifications that extend its half-life after subcutaneous injection to 13–15 h, allowing for once-daily dosing. In contrast to previous centrally acting OMs, the adverse effect profile of GLP-1RAs is predominantly gastrointestinal, with nausea, diarrhea, constipation, vomiting, and dyspepsia being most commonly reported [21].

Across clinical trials, orlistat, phentermine/topiramate, naltrexone/bupropion, and liraglutide each demonstrate weight loss typically in the range of 5%–10% of baseline body weight (5%–8% in excess of placebo) at around 1 year [11, 16, 19, 22, 23]. These therapies also share downstream metabolic benefits including improvements in glycaemia, lipid profile, and blood pressure, although specific advantages differ. While these agents facilitate mean weight losses of a significantly greater magnitude than lifestyle interventions alone, with a favorable

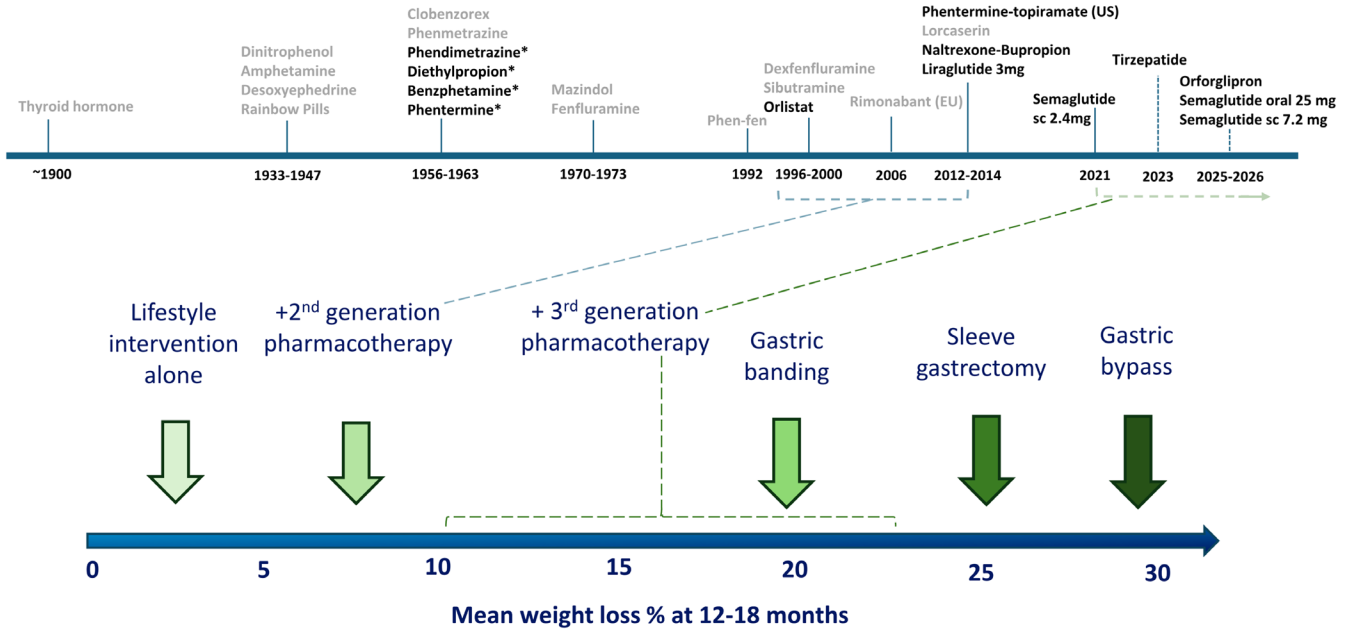

FIGURE 1 | Overview of medications used for obesity management since early 20th century EU, European Union, US, United States of America; * indicates approved by FDA for short-term use. Gray indicates medications withdrawn from market or no longer approved for obesity management.

safety profile relative to first-generation OMs, there is still a wide gap in overall efficacy compared with metabolic bariatric surgeries (Figure 1). This gap in weight and health outcomes is starting to be filled by the latest generation of OMs [12, 15, 24–27] (Table 1).

Additionally, setmelanotide is a MC4R agonist approved for the treatment of monogenic forms of obesity due to pathogenic mutations in the MC4R pathway, including loss of function of the receptors for POMC, leptin, or proprotein convertase subtilisin/kexin type 1 (PCSK1), and for treatment of obesity and control of hunger in adults and children aged 4 years and older with acquired hypothalamic obesity, and those aged 2 years and older with Bardet-Biedl syndrome. Two single-arm, open-label, Phase 3 clinical trials with 10 participants with POMC deficiency and 11 participants with leptin receptor deficiency show that 80% and 45% achieved weight loss of at least 10% at approximately 1 year, respectively, primarily driven by reductions in hunger [28]. An additional placebo-controlled Phase 3 trial in participants with acquired hypothalamic obesity reported a reduction in BMI of 16.5% after 52 weeks of setmelanotide in adult participants (from mean baseline 41 kg/m^2) and a BMI gain of 3.3% with placebo [29]. The adverse effects most common included injection site reactions and hyperpigmentation, nausea, and vomiting [28, 29].

3.2 | Third-Generation OMs

3.2.1 | Semaglutide

Approved by the FDA for chronic weight management in 2021, semaglutide is the first of a new generation of highly effective incretin-based OMs. It is a synthetic GLP-1RA with an extended half-life of 165 h, which allows for once-weekly subcutaneous dosing. Data from Phase 3 clinical trials of semaglutide 2.4 mg weekly showed mean weight loss of 14.9% from baseline at 68 weeks in people without T2D, which was 12.4% higher than placebo [30]. Furthermore, more than two-thirds of participants in the semaglutide group achieved weight loss of 10% or more (69% vs. 12% placebo) and half lost 15% or more of body weight (51% vs. 5% placebo; $p < 0.001$ for both comparisons) [30]. Improvements in cardiometabolic markers also prevailed in the semaglutide group, including in glycated hemoglobin levels, lipid profile, blood pressure, and waist circumference [30–32].

A subsequent study directly comparing semaglutide 2.4 mg weekly with liraglutide 3.0 mg daily showed a mean body weight loss of 15.8% from baseline to 68 weeks with semaglutide, compared to 6.4% for liraglutide [33]. There were similar rates of adverse events between the groups, which were mostly gastrointestinal related, and consistent with previous trials of GLP-1RAs. However, treatment discontinuation was twice as common in the liraglutide group (28%) compared to semaglutide (14%), with reasons such as shorter half-life, leading to a more noticeable return in hunger when pausing treatment, and a daily dosing regimen, postulated to contribute [33].

In December 2025, an oral formulation of semaglutide (25 mg daily) was the first oral GLP-1RA approved by the FDA for weight management, after publication of Phase 3 clinical trial data showing mean weight loss of 13.6% at 64 weeks (estimated treatment difference vs. placebo of −11.4%), with 60% of oral semaglutide-treated participants (vs 14% with placebo) reaching weight loss of 10% or more [34]. Additionally, high-dose subcutaneous semaglutide 7.2 mg weekly has been approved following the STEP-UP trial [35]. Participants who received semaglutide 7.2 mg weekly had greater weight loss at 72 weeks compared to those who received semaglutide 2.4 mg weekly (estimated treatment difference −3.1% (95% CI −4.7 to −1.6, $p < 0.0001$)) and placebo (estimated treatment difference −14.8% (95% CI −16.2 to −13.4, $p < 0.0001$)) [35].

TABLE 1 | Key characteristics of approved obesity medications.

Medication	Mechanism	Dose	Key clinical trial	Mean weight loss	Most common adverse effects	Indications beyond chronic weight management	Regulatory approval for chronic weight management
Tirzepatide	Dual GLP1 + GIP receptor agonist	Starting dose: 2.5 mg weekly, titrate up to 15 mg weekly	SURMOUNT-1 [36] 72 weeks, 2539 adults, 1:1:1:1 to tirzepatide 5, 10, 15 mg or placebo BMI > 30 or BMI ≥ 27 with weight related complication	Placebo: 3.1% 5 mg: 15.0% 10 mg: 19.5% 15 mg: 20.9%	Nausea, vomiting, diarrhea, constipation	T2D OSA with obesity	FDA EMA Others including TGA (Australia)
Semaglutide	GLP1 receptor agonist	Subcutaneous: starting dose: 0.25 mg weekly, titrate up to 2.4 mg weekly	STEP 1 [30] 68 weeks, 1961 adults, 2:1 to semaglutide 2.4 mg or placebo BMI > 30 or BMI ≥ 27 with weight related complication	Placebo: 2.4% Semaglutide 2.4 mg: 14.9%	Nausea, vomiting, diarrhea, constipation	T2D CKD and CVD risk reduction in T2D + CKD CV risk reduction in obesity without T2D MASH with moderate to advanced fibrosis	FDA EMA Others including TGA (Australia)
		Subcutaneous: up to 7.2 mg weekly	STEP-UP [35] 72 weeks, 1407 participants, 5:1:1 to semaglutide 7.2 mg, semaglutide 2.4 mg or placebo BMI > 30	Placebo: 3.9% Semaglutide 2.4 mg: 15.6% Semaglutide 7.2 mg: 18.7%	As for semaglutide 2.4 mg	None	FDA
		Oral: Starting dose: 3 mg daily, titrate up to 25 mg daily	OASIS-4 [34] 64 weeks, 307 adults, 2:1 to semaglutide 25 mg or placebo BMI > 30 or BMI ≥ 27 with weight related complication	Placebo: 2.2% Semaglutide 25 mg: 13.6%		CV risk reduction in obesity without T2D	FDA
Orforglipron	GLP1 receptor agonist	Oral, starting dose 0.8 mg daily, titrate up to max 17.2 mg	ATTAIN-1 [38] 72 weeks, 3127 adults, 3:3:3:4 to orforglipron 6, 12, 36 mg or placebo BMI > 30 or BMI ≥ 27 with weight related complication	Placebo 2.1% 12 mg: 7.5% 24 mg: 8.4% 36 mg: 11.2%	Nausea, vomiting, diarrhea, constipation	None	FDA

(Continues)

TABLE 1 | (Continued)

Medication	Mechanism	Dose	Key clinical trial	Mean weight loss	Most common adverse effects	Indications beyond chronic weight management	Regulatory approval for chronic weight management
Liraglutide	GLP1 receptor agonist	Starting dose: 0.6 mg daily, titrate up to 3.0 mg daily	SCALE [23] 56 weeks, 3731 adults, 2:1 to liraglutide or placebo BMI > 30 or ≥ 27 with dyslipidaemia or hypertension	Placebo: 2.6% Liraglutide: 8.0%	Nausea, vomiting, diarrhea, constipation	T2D CV Risk reduction in T2D	FDA EMA Others including TGA (Australia)
Orlistat	Reversible inhibitor of gastrointestinal lipase	120 mg with meals	[11] 52 weeks, 688 participants completed lead-in period with hypocaloric diet, then randomized 1:1 to orlistat or placebo	Placebo: 6.1% (note hypocaloric lead in period) Orlistat: 10.2%	Steatorrhea, fecal incontinence/ urgency, reduction in fat soluble vitamin absorption	None	FDA EMA Others including TGA (Australia)
Phentermine/ Topiramate	Phentermine: Sympathomimetic, Topiramate: Mechanism unknown for weight loss, inhibits carbonic anhydrase, increases GABA activity	Starting dose 3.75/23 mg, titrate up to 15 mg/92 mg daily	CONQUER [16] 56 weeks, 2487 participants, 2:1:2 to Phentermine/ Topiramate 15 mg/92 mg, Phentermine/Topiramate 7.5 mg/46 mg, or placebo BMI > 30 or BMI ≥ 27 with weight related complication	Placebo: 1.2% Phentermine/ Topiramate 7.5 mg/46 mg: 7.8% Phentermine/ Topiramate 15 mg/92 mg: 9.8%	Paraesthesia, dry mouth, constipation, tachycardia	None	FDA
Naltrexone/ Bupropion	Bupropion: Reuptake inhibitor of noradrenaline and dopamine, stimulating POMC neurons Naltrexone: Opioid antagonist, blocks beta endorphin mediated inhibitor feedback on POMC neurons	Starting dose: 8 mg/90 mg daily, titrate up to 32 mg/360 mg daily	COR-I [19] 56 weeks, 1742 adults, 1:1:1 to NB32, NB16 or placebo BMI 30–45 or 27–45 with dyslipidemia or hypertension	Placebo: 1.3% NB16: 5.0% NB32: 6.1%	Nausea, constipation, headache, insomnia	None	FDA EMA Others including TGA (Australia)

Abbreviations: BMI, Body Mass Index; CKD, chronic kidney disease; CV, cardiovascular; EMA, European Medicines Agency; FDA, Food and Drug Administration; GABA, gamma-aminobutyric acid; GIP, glucose dependent insulinotropic polypeptide; GLP1, glucagon-like-peptide 1; MASH, metabolic dysfunction associated steatohepatitis; NB, naltrexone/bupropion; OSA, obstructive sleep apnoea; POMC, pro-opiomelanocortin; SC, subcutaneous; T2D, type 2 diabetes; TGA, Therapeutic Goods Administration.

3.2.2 | Tirzepatide

Tirzepatide is a once weekly subcutaneous peptide with dual agonist activity at GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) receptors [36]. In a Phase 3 clinical trial in people without T2D, tirzepatide led to superior weight loss compared to placebo at 5, 10 and 15 mg weekly (15%, 19.5%, 20.9%, respectively vs. 3.1% placebo) over 72 weeks [36]. Tirzepatide also had significant benefits with respect to waist circumference, blood pressure, glycaemia and lipid levels [36].

An open label RCT directly comparing maximum tolerated doses of tirzepatide (up to 15 mg) and semaglutide (up to 2.4 mg) once-weekly over 72 weeks found tirzepatide to be superior for mean total weight loss (20.2%, [95% CI, 19.1 to 21.4] vs. 13.7%, [95% CI, 12.6 to 14.9]) [37]. Furthermore, participants in the tirzepatide group were more likely to achieve weight loss of at least 10%, 15%, 20%, and 25% [37]. Adverse effects were most commonly gastrointestinal in nature, occurred primarily during periods of dose escalation and rates were similar in both treatment arms, but injection site reactions were notably more common with tirzepatide (8.6% vs. 0.3%) [37].

3.2.3 | Orforglipron

Orforglipron is a once-daily non-peptide oral GLP-1RA. A 72 week trial of 3127 participants with obesity without T2D found a mean loss in body weight of 7.5% to 11.2% for doses of 6 to 36 mg daily, compared with 2.1% in the placebo group ($p < 0.001$ for all comparisons with placebo) [38]. In the 36 mg group, 54.6% had a reduction of 10% or more body weight, 36.0% had a reduction of ≥ 15% and 18.4% had a reduction of ≥ 20% body weight, compared to 12.9%, 5.9% and 2.8% (respectively) with placebo [38]. Furthermore, there were improvements in waist circumference, triglyceride levels, non-HDL cholesterol and systolic blood pressure with orforglipron. Consistent with the known adverse effects of GLP1RAs, most adverse effects were gastrointestinal and mild to moderate in severity [38]. Orforglipron was approved by the FDA for obesity management in December 2025 and has been recommended for approval by the European Medicines Agency at the time of writing.

3.2.4 | Treatment Duration

Clinical trials with up to 3–4 years' follow-up show that new incretin agents can facilitate sustained weight reduction and cardiometabolic benefits with continued treatment [39, 40]. As expected in chronic disease management, cessation of treatment results in loss of therapeutic effect, with regain in weight and deterioration in blood pressure, lipid profile and health-related quality of life [41, 42]. Evidence from recent clinical trials indicates that after the initial weight reduction phase using standard treatment doses of once-weekly subcutaneous tirzepatide and/or semaglutide, reducing the tirzepatide dose or switching to orforglipron may enable maintenance of weight loss in some individuals [43, 44].

3.2.5 | Gastrointestinal Adverse Effects

The most common adverse effects associated with incretin OMs are gastrointestinal [45]. Nausea, vomiting, constipation and diarrhea are the most frequently reported effects, which tend to be most prominent after treatment initiation and dose escalation [46]. Although such effects are usually mild, they can be sufficiently bothersome to lead to treatment discontinuation. In the STEP-1 trial, a greater proportion of participants discontinued semaglutide 2.4 mg weekly compared to placebo due to gastrointestinal adverse events (7.0% vs. 3.1%) [30]. In this study, nausea was reported in 44.2% of semaglutide (vs. 17.4% placebo) participants, vomiting in 24.8% (vs. 6.6%), and diarrhea in 31.5% (vs. 15.9%) [30].

There has been concern about the peri-procedural implications of the physiological action of GLP-1RA on inhibition of gastric emptying, which could increase the risk of retained gastric contents and, potentially, pulmonary aspiration. A meta-analysis of current data found an increased risk of presenting with residual gastric contents despite appropriate fasting among patients using incretin medications (odds ratio [OR] 5.96, 95% CI 3.96–8.98) but this did not translate to an increased risk of pulmonary aspiration (OR 1.04, 95% CI 0.87–1.25) [47]. Multi-society clinical guidelines recommend against withholding incretin treatment pre-operatively due to the consequent risk of perioperative hyperglycaemia, which itself may slow gastric emptying, as well as being associated with increased morbidity [48, 49]. Instead, a clear fluid diet on the day prior to the procedure, with standard 6-h fasting on the day of surgery, is recommended [48, 49]. This approach is supported by an RCT of 60 participants undergoing upper endoscopy, which found that no patients who underwent a clear liquid diet the day before the procedure had clinically significant retained gastric contents [50].

GLP-1RAs increase pancreatic enzyme secretion, hence elevated circulating levels of amylase and lipase are common in people treated with GLP-1RA. As such, whether incretin medications are associated with pancreatitis has been a longstanding question, with a signal persisting in pharmacovigilance analysis, but not reflected in RCTs, meta-analyses and real world studies [51, 52]. Pharmacovigilance analysis of the FDA Adverse Event Reporting System (FAERS) database (2007–2023) shows a signal toward acute pancreatitis across GLP-1 receptor agonists, particularly with exenatide [53]. In contrast, meta-analyses of seven cardiovascular outcome trials have demonstrated no association between GLP-1 agonist use and acute pancreatitis (pooled OR 1.05 95% CI 0.78–1.41, $p = 0.75$) [54]. Regulatory authorities recommend caution with using incretin medications in people with a history of pancreatitis, to discontinue treatment if pancreatitis is suspected and to not restart therapy if the diagnosis is confirmed [55–57].

Both obesity, and weight reduction are known to be associated with cholelithiasis. This risk is observed also with incretin-based medications. A systematic review encompassing 76 RCTs of obesity and T2D found that participants receiving GLP-1RAs had a 37% increased relative risk of developing gallbladder disease compared to control (placebo or active comparator), including increased risks of cholelithiasis, cholecystitis and

cholecystectomy, but not biliary cancer [58]. This was more pronounced with longer treatment duration and higher GLP-1RA dose [58]. There are likely multiple mechanisms that underlie this risk, including the inhibition of cholecystokinin secretion, which leads to impairment of gallbladder contraction and subsequent biliary stasis, increasing the likelihood of gallstone formation [59]. Additionally, GLP1RAs can increase biliary cholesterol saturation, further favoring gallstone formation. Rapid weight loss compounds these effects, increasing the risk of biliary stasis and subsequent cholelithiasis [59].

Appropriate patient selection prior to initiating incretin medications includes consideration of contraindications, such as a personal or family history of medullary thyroid carcinoma, Multiple Endocrine Neoplasia syndrome type 2, and pregnancy [60]. Following commencement, ongoing follow-up is needed for monitoring of progress toward and (maintenance of) treatment goals, and to optimize tolerability and safety. Patients should be educated on adverse effects, and multidisciplinary support, including dietitian input if available, should also be considered [60]. Identification of suboptimal dietary patterns, ensuring adequate protein, fiber and micronutrient intake, and strategies to preserve lean mass, including resistance training, are important components of therapy [61].

4 | From Obesity Medications to Cardiometabolic Medications

Beyond their effects on lowering blood glucose and body weight, medications with GLP-1RA activity are well-established to reduce rates of cardiovascular events and adverse kidney outcomes in high-risk populations with T2D [62]. Evidence is growing that these cardioprotective and renoprotective actions extend also to cohorts without T2D, in addition to beneficial effects of these agents on a host of other obesity-related diseases, including metabolic-dysfunction associated steatotic liver disease (MASLD) and steatohepatitis (MASH) [62].

The SELECT trial of 17 604 people with overweight/obesity and established cardiovascular disease but without T2D showed that semaglutide 2.4 mg weekly led to a 20% reduction in a composite major adverse cardiovascular event (MACE) outcome of death from cardiovascular causes, non-fatal myocardial infarction and stroke over a mean follow-up of 39.8 months (hazard ratio 0.80 [95% CI 0.72 to 0.90]) [39]. Numerous cardiovascular risk factors were also reduced, including body weight, blood pressure, glycaemic control, lipid profile, and C-reactive protein [39]. Early separation of MACE event rates between groups and the lack of relationship between early weight loss and MACE risk indicates that cardioprotective effects are at least partly weight-independent [63]. The mechanisms by which these effects occur are not completely understood, but may include improvements in endothelial function, oxidative stress and inflammation [64]. These landmark findings led to semaglutide being the first OM to receive regulatory approval for cardiovascular risk reduction.

A post hoc analysis of the SELECT trial indicates a renoprotective effect of semaglutide in people without T2D, with a 22% reduction in a composite endpoint of death from kidney disease, initiation of chronic kidney replacement therapy, onset of persistent eGFR $<15\,mL/min/1.73\,m^2$, persistent $\geq 50\%$ reduction in eGFR or onset of persistent macroalbuminuria [65]. These findings are supported by an RCT of participants with overweight/obesity and non-diabetic chronic kidney disease, in which semaglutide 2.4 mg weekly led to a $>50\%$ reduction in albuminuria [66].

Both semaglutide 2.4 mg weekly and tirzepatide have demonstrated improvements in symptoms, quality of life, and physical function in people with overweight/obesity and heart failure with preserved ejection fraction (HFpEF) [67, 68]. Compared to placebo, tirzepatide also reduced the rate of a composite of worsening heart failure events and death from cardiovascular causes (HR 0.62 [95% CI 0.41 to 0.95]), driven by a reduction in worsening heart failure [67].

Outside of cardiorenal outcomes, tirzepatide improves outcomes in obstructive sleep apnoea (OSA) both with and without continuous positive airway pressure treatment, [69] resulting in it being the first medication approved for the treatment of moderate-to-severe OSA in people with obesity. Furthermore, in participants with overweight/obesity and symptomatic knee osteoarthritis, treatment with once-weekly semaglutide 2.4 mg resulted in improvements in pain and physical function along with weight loss of 10.5% in excess of placebo [70].

4.1 | Metabolic Dysfunction-Associated Steatotic Liver Disease and Steatohepatitis

MASH is characterized by fat accumulation in the liver, associated with inflammation and hepatocyte injury. Growing evidence suggests disease-modifying properties of incretin medications in MASH (Table 2).

The ESSENCE Phase 3 RCT is evaluating semaglutide 2.4 mg weekly in 1197 participants with biopsy-confirmed MASH with moderate to advanced fibrosis. At baseline, 31% of participants had stage F2 fibrosis and 69% had F3 fibrosis [71]. The study is ongoing, with a planned interim analysis at 72 weeks showing resolution of steatohepatitis without worsening of liver fibrosis in 63% of semaglutide-treated participants (vs. 34% with placebo, $p<0.001$) and a reduction in liver fibrosis by ≥ 1 stage without worsening of steatohepatitis in 37% (vs. 22%, respectively) [71]. On this basis, in 2025, semaglutide was approved by the FDA to treat MASH in people with moderate-to-advanced fibrosis.

An earlier Phase 2 trial (LEAN) indicated a benefit of liraglutide 1.8 mg subcutaneously once daily in 52 participants with MASH, 54% of whom had stage F0-F2 fibrosis, and 46% F3-F4 fibrosis. After 48 weeks of treatment, 39% of participants randomized to receive liraglutide had resolution of MASH with no worsening of fibrosis compared to 9% in the placebo arm [72].

Promising Phase 2 trial data from the SYNERGY-NASH trial indicate that tirzepatide may also have benefits in this condition [73]. A total of 190 participants with biopsy-confirmed MASH and F2 (43%) or F3 (57%) fibrosis were randomized to receive once weekly tirzepatide or placebo for 52 weeks. Among participants receiving tirzepatide 5, 10, and 15 mg, 44%, 56%, and 62% (respectively) met the criteria for resolution of MASH

TABLE 2 | Incretin medications in MASLD.

Trial and duration	Medication	Participants	Baseline fibrosis stages	Liver endpoint	Outcome: NASH/MASH resolution without worsening of fibrosis	Other liver outcome
LEAN Phase 2 48 weeks	Liraglutide 1.8 mg daily (GLP-1 receptor agonist)	$N=52$ Liraglutide 1.8 mg: 26 Placebo: 26	Liraglutide group: F0-F2: 54% F3-F4: 46% Placebo group: F0-F2: 42% F3-F4: 58% Note: F4 (cirrhosis) included	Histological endpoints: Resolution of NASH/MASH without worsening of fibrosis Improvement in Kleiner Fibrosis Stage	Liraglutide 1.8 mg: 39% Placebo: 9%	Improvement in Kleiner Fibrosis Stage Liraglutide: 26%, Placebo: 14% ($p=0.46$) Worsening in Kleiner Fibrosis Stage: Liraglutide: 9%, Placebo: 36%, ($p=0.04$)
ESSENCE Phase 3 72 weeks	Semaglutide 2.4 mg weekly (GLP-1 receptor agonist)	$N=1197$ Pre-planned interim analysis of first 800 patients: Semaglutide 2.4 mg: 534 Placebo: 266	F2: 31.3% F3: 68.8%	Histological endpoints: Resolution of MASH without worsening of fibrosis Improvement in fibrosis ≥1 stage without worsening of MASH	Semaglutide 2.4 mg: 62.9% Placebo: 34.3%	Reduction in liver fibrosis ≥1 stage without worsening of steatohepatitis Semaglutide 2.4 mg: 36.8% Placebo: 22.4%
SYNERGY-NASH Phase 2 52 weeks	Tirzepatide 5 mg/10 mg/15 mg (GLP-1/GIP receptor agonist)	$N=190$ 5 mg $n=47$ 10 mg $n=47$ 15 mg $n=48$ Placebo $n=48$	F2: 43% F3: 57%	Histological endpoint Resolution of MASH without worsening of fibrosis	5 mg: 44% 10 mg: 56% 15 mg: 62% Placebo: 10%	Reduction in liver fibrosis ≥1 stage without worsening of MASH Tirzepatide 5 mg: 55% 10 mg: 51% 15 mg: 51% Placebo: 30%
Phase 2 (substudy) 48 weeks	Retatrutide 1 mg/4 mg/8 mg/12 mg (GLP-1/GIP/Glucagon receptor agonist)	$N=98$ 1 mg $n=20$ 4 mg $n=19$ 8 mg $n=22$ 12 mg $n=18$ Placebo $n=19$	Fibrosis stage not available. Inclusion ≥10% liver fat	Radiological endpoint Mean relative change in liver fat (baseline to 48 weeks)	Not available	Relative change in liver fat 1 mg: −51.3% 4 mg: −59.0% 8 mg: −81.7% 12 mg: −86.0% Placebo: −4.6%

(Continues)

TABLE 2 | (Continued)

Trial and duration	Medication	Participants	Baseline fibrosis stages	Liver endpoint	Outcome: NASH/MASH resolution without worsening of fibrosis	Other liver outcome
SYNCHRONIZE-MASLD 48 weeks	Survodutide 6.0 mg (GLP-1/Glucagon receptor agonist)	$N = 216$ Survodutide 6.0 mg $n = 146$ Placebo $n = 70$	9.7% of participants with biopsy confirmed MASH (F0-F3) Note: Not all participants had liver biopsy	Radiological endpoint: Participants with ≥ 30% reduction in magnetic resonance imaging proton density fat fraction assessed liver fat content	Not available	Radiological endpoint as defined: (Efficacy estimand) 6.0 mg: 84.2% Placebo: 24.3% Change in liver fat content 6.0 mg: −58.7% Placebo: −9.5%

Abbreviations: F, fibrosis stage; GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide-1; MASH, metabolic dysfunction-associated steatohepatitis; MRI, magnetic resonance imaging; NASH, Non-alcoholic steatohepatitis (historical terminology, now superseded by MASH); THR-β, thyroid hormone receptor beta.

without worsening of fibrosis, compared with 10% in the placebo group [74].

Liver-specific clinical trials are also being conducted for OMs under development. Incretin agents with glucagon receptor agonist action may be particularly beneficial for hepatic lipid clearance due to the effects of glucagon on promoting fatty acid oxidation [75].

The triple GLP-1/GIP/glucagon receptor agonist retatrutide was evaluated in a sub-analysis of 98 participants with ≥ 10% liver fat content by MRI in a Phase 2 obesity trial [76]. In this analysis, liver fat reductions at 48 weeks for the 1 mg, 4 mg, 8 mg and 12 mg groups were −51.3%, −59.0%, −81.7% and −86.0%, respectively, compared with −4.6% in the placebo group [76]. Notably, this sub study used radiological rather than histological end points, and participants were not stratified by liver fibrosis stage, limiting comparability with other MASH trials. An ongoing clinical trial (SYNERGY-OUTCOMES, NCT07165028) is examining whether retatrutide and tirzepatide (vs placebo) can prevent major adverse liver outcomes in adults with high-risk MASLD. The study aims to enroll ~4500 participants, followed over approximately 224 weeks, with a composite primary endpoint of progression to cirrhosis, development of varices, ascites or hepatic encephalopathy, variceal hemorrhage, increase in model for end-stage liver disease (MELD) from ≤ 12 to ≥ 15, liver transplantation and all-cause mortality.

The effects of the dual GLP-1/glucagon receptor agonist survodutide 6 mg weekly on the co-primary endpoints of ≥ 30% reduction in liver fat content and change in body weight were recently examined in the SYNCHRONIZE-MASLD Phase 3 placebo-controlled RCT [77]. This study included 216 adults with overweight/obesity and "at-risk" MASLD, defined by evidence of liver inflammation and/or fibrosis by non-invasive tests, or biopsy-confirmed MASH. After 48 weeks, mean weight reduction was 8.7% for survodutide (vs. 1.4%, placebo), while 69% of survodutide-treated participants (vs. 29% placebo) had ≥ 30% reduction in liver fat content, as assessed by magnetic resonance imaging-proton density fat fraction (MRI-PDFF), using the treatment regimen estimand. The mean change in liver fat content was −58.7% with survodutide, and −9.5% with placebo, with 61% of survodutide (and 6% placebo) participants reaching a liver fat content of < 5% at week 48, (efficacy estimand) [77]. The effects of survodutide at doses of 2.4, 4.8 and 6.0 mg in adults with biopsy confirmed MASH and fibrosis F1 (24%), F2 (41%), or F3 (35%) were assessed in a Phase 2 trial. Improvements in MASH without worsening of fibrosis were seen in 47% of participants in the 2.4 mg group, 62% in the 4.8 mg group and 43% in the 6.0 mg group, compared to 14% in the placebo group ($p < 0.001$) [78]. Phase 3 trials are underway assessing participants with confirmed MASH and stage F2 or F3 liver fibrosis (NCT06632444) as well as cirrhosis (NCT06632457) [79].

Although no head-to-head trials have been conducted, the ESSENCE (semaglutide 2.4 mg, 62.9%) and SYNERGY-NASH trials (tirzepatide 15 mg, 62%), both showed substantially higher rates of MASH resolution without worsening of fibrosis compared to resmetirom, an oral liver directed thyroid hormone receptor beta selective agonist [71, 73]. Resmetirom was the first approved medication (FDA 2024) for the treatment of MASH.

The MAESTRO-NASH trial demonstrated MASH resolution without worsening of fibrosis in 25.9% and 29.9% of participants with resmetirom 80 and 100 mg, respectively, compared to 9.7% with placebo across cohorts with broadly similar fibrosis groups and BMI at baseline, noting cross trial comparisons always need to be interpreted with caution [80].

5 | Emerging Therapeutic Agents

There are multiple agents currently in development, which target receptors for incretin and other gut hormones (including glucagon, amylin) as well as additional pathways aimed at minimizing muscle loss during weight loss. Agents in Phase 3 clinical trials for obesity are summarized below.

Retatrutide is a triple agonist at GLP1, GIP and glucagon receptors for which an extensive Phase 3 clinical trial program is ongoing [81]. In a phase 2 RCT of 338 participants with overweight/obesity, body weight loss of 17%–24% was reported for the target doses of 4 to 12 mg once-weekly, compared to 2.1% with placebo at 48 weeks [81]. At the 12 mg dose, 90% of participants lost greater than 10% body weight, half lost greater than 25% and a quarter lost 30% or more. Noting that Phase 2 trials are not powered for efficacy outcomes, this level of weight loss is promising and has only previously been observed with bariatric surgery [82]. Notably, weight loss did not appear to plateau at 48 weeks and the Phase 3 trials underway have a longer duration of 68 weeks or more [83]. Substantial improvements in waist circumference, blood pressure and glycaemia were also observed [81]. At 36 weeks, there was a mean reduction of −8.8 mmHg in systolic blood pressure (retatrutide 12 mg) compared with −2.9 mmHg in the placebo group, with discontinuation of at least one antihypertensive medication seen in 30% of participants taking retatrutide 12 mg weekly. At 48 weeks, waist circumference had reduced by a mean of 20.6 cm in the 12 mg retatrutide group, compared to 2.4 cm in the placebo group. Furthermore, in this participant cohort without T2D, HbA1c reductions of 0.4%–0.5% were seen in the high dose retatrutide groups, compared to 0% in the placebo arm [81]. Adverse effects with retatrutide were dose related and predominantly gastrointestinal in nature [81].

Amylin is a pancreatic hormone co-synthesized and released with insulin [84]. It reduces energy intake by increasing satiation via actions on the amylin receptor in the hindbrain, hypothalamus and mesolimbic dopamine system [84]. Cagrilintide is an amylin analog delivered as a once-weekly subcutaneous injection, with Phase 2 trial data over 26 weeks showing bodyweight loss of 8% and 2% greater than placebo and liraglutide, respectively [85]. A Phase 3 RCT investigated the combination of cagrilintide with semaglutide (CagriSema) on body weight in 3417 participants with obesity [86]. Those randomized to CagriSema achieved a weight loss of 20.4%, compared with 3% in the placebo group, and 11.5% and 14.9% allocated to receive cagrilintide and semaglutide monotherapy [86]. A further study was conducted in participants living with obesity and T2D [87], which found 13.7% weight loss with CagriSema and 3.4% with placebo, in keeping with the well-described phenomenon of less weight loss in people with T2D. Nonetheless, improvements in cardiovascular risk factors were impressive, with an estimated mean difference compared with placebo of −8.3 cm in waist circumference (95% CI −9.3 to −7.3), −1.4% difference in HbA1c (95% CI −1.6 to −1.2) and −4.1 mmHg in systolic blood pressure (95% CI, −6.0 to −2.1) [87]. Most of the adverse effects were gastrointestinal in nature and were transient [87].

Survodutide is a dual agonist of GLP-1 and glucagon receptors in clinical trials for obesity at doses of 3.6 and 6.0 mg subcutaneously weekly [88]. In a recent Phase 3 trial, 725 participants were randomized to receive a 3.6 mg dose, 6.0 mg dose, or placebo. At week 76, the mean change in body weight from baseline was −12.2% (−13.6 to −10.8) in the 3.6 mg group, −13.0% (−14.4 to −11.6) in the 6.0 mg group, and −5.4% (−6.9 to −4.0) in the placebo group [89]. Gastrointestinal side effects affected 80.9% of participants in the 3.6 mg group, 89.7% in the 6.0 mg group, and 47.9% in the placebo group [89]. Data on the hepatic effects of survodutide is described in the section on MASLD/MASH.

6 | Future Perspectives

Safely achieving and maintaining substantial weight loss and health improvements—long-elusive goals of obesity management—are increasingly reachable due to tremendous progress in drug development. This progress has already begun to benefit the health of many people living with obesity and related diseases [90] but questions and challenges remain.

All current approaches to obesity management lead to loss of lean mass, typically representing around 25% of total weight lost but may be greater with larger weight losses [91]. Whether this adversely affects muscle quality and function is an unresolved question, [92] but in any case, many new therapeutic approaches and targets are being explored, aiming to optimize body composition (i.e., maximize fat loss and minimize loss of muscle) during weight loss [93, 94].

Furthermore, more effective OMs raise the possibility of excessive weight loss and necessitate definition of appropriate treatment targets, which have not previously been agreed-upon in obesity management [95].

Implementation of effective obesity care more widely and equitably in clinical practice will require sustainable long-term funding models for provision of OMs and co-ordinated multidisciplinary care. Importantly, greater availability and efficacy of OMs will not replace the need to optimize nutrition and physical activity, but the role of nutritional management in particular is likely to shift to align with the goals of nutritional management after bariatric surgery (i.e., from driving weight loss to optimizing nutritional quality when appetite is reduced) [96].

7 | Conclusion

Advances in obesity pharmacotherapy have led to the development of medications that deliver benefits not only for weight loss, cardiovascular risk factors, and quality of life, but also cardio-renal-metabolic outcomes. Newer agents are achieving larger and more durable reductions in body weight and improvements in health. These disease-modifying

cardiometabolic therapies may play an increasing role in chronic disease management as the global burden of obesity and its complications continues to rise. Current challenges include defining optimal treatment targets and devising cost-effective and sustainable funding models to support implementation of care for priority populations.

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Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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