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REVIEW

Pharmacotherapy for Obesity: Recent Updates

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Abstract: In this narrative review we describe the recent updates regarding anti-obesity medications as of February 2025. We describe the physiologic mechanisms underpinning the development of hunger, satiation, and maintenance of satiety to address targets for anti-obesity medications. The efficacy, mechanism, and additional beneficial effects of anti-obesity medications are then further detailed. For this review, we focus on FDA-approved medications for obesity and on select medications currently under development and undergoing Phase 2 and 3 trials. We start by focusing on the non-incretin anti-obesity medications orlistat, phentermine, phentermine-topiramate, and naltrexone-bupropion. We also highlight setmelanotide for heritable obesity. The mechanism of action and comparative efficacy of the GLP-1 receptor agonists liraglutide and semaglutide are reviewed. Tirzepatide, the GLP-1 and GIP-receptor dual agonist is described, and weight loss is compared to alternative anti-obesity medications. Additional incretin targets in the pipeline include dual co-agonists to glucagon and GLP-1 receptors, triple agonists targeting glucagon, GLP-1 and GIP, novel GLP-1 agonists, oral formulations of GLP-1 agonists, and amylin agonists. Finally, we provide best practices for adjuncts to pharmacologic treatments of obesity, monitoring efficacy of obesity treatments, and adjusting medication regimens for providers.

Keywords: obesity, pharmacotherapy, glucagon-like peptide-1, obesity management

Introduction

Obesity remains a disease of epidemic proportions, with up to 43% of the United States population affected and rates worldwide doubling from 1990 to 2022.[1,2] This rising prevalence of obesity brings significant costs to the healthcare system, estimated to be up to $172 billion in annual expenditures.[3]

Obesity is a disease of excess adiposity, but the diagnostic criteria remain an area of debate.[4] Obesity has traditionally been classified based upon body mass index (BMI), as described in Table 1.[5] BMI is a simple and reliable, population-based, metric for measuring body size, but comes with limitations for identifying individuals at increased risk of complications of obesity, particularly within different ethnic groups.[6] Additional methods of measuring adiposity are detailed in Table 1. Most studies investigating obesity treatments rely on BMI, which will be the criterion used in this paper.

Untreated obesity is associated with significant additional health consequences (Figure 1),[7,15–29] and obesity is an independent risk factor for increased all-cause mortality.[30] The 2013 joint American Heart Association (AHA), Obesity Society (TOS) and American College of Cardiology (ACC) guidelines for management of overweight and obesity state that "the greater the BMI, the higher the risk of fatal coronary heart disease" and "that the higher the BMI, the greater the risk of all-cause mortality".[31,32] Additionally, "overweight and obese adults with type 2 diabetes who intentionally lost 9 kg to 13 kg had a 25% decrease in mortality rate" and "there is a dose–response relationship between the amount of weight loss achieved by lifestyle intervention and the improvement in lipid profile". Thus, treatments aimed at both correcting weight management and optimizing metabolic risk profiles can have the largest benefit in improving health outcomes.

At a fundamental level, obesity arises from caloric imbalance where intake exceeds expenditure. Food intake regulation and signaling between the gut-adipose-brain axis are important targets for treatment of obesity.[33] Historically, options for treatment of obesity focused on dietary modification and exercise.[34] Many of the comorbidities associated with obesity can be effectively managed with a sustained 5–10% body weight loss, which is a reasonable first step for most patients.[35] Bariatric surgical options, which result in more than 25% total body weight loss, are not widely adopted due to costs and side effect profile.[36,37]

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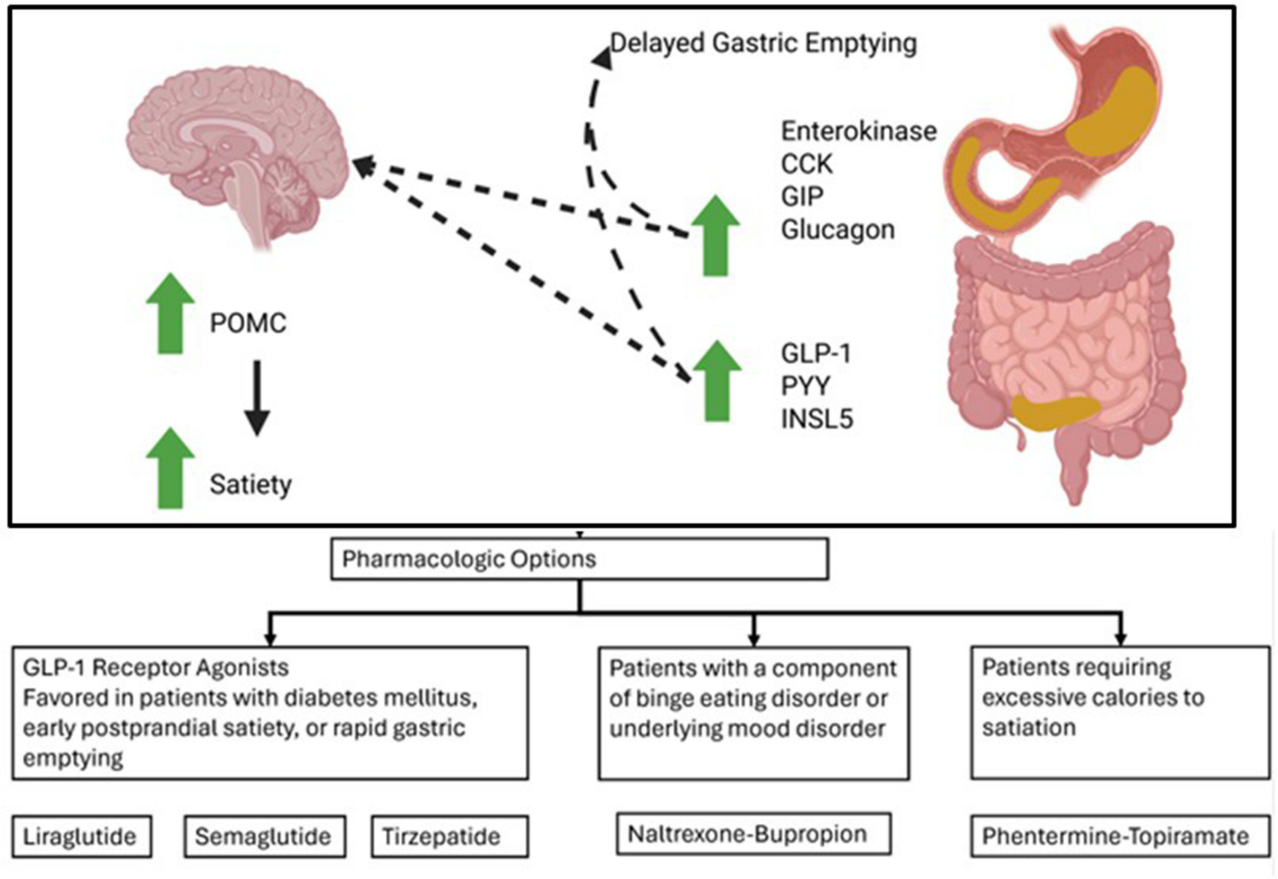
Graphical Abstract



Fortunately, there has been substantial expansion of pharmacological therapies for obesity in the last decade. In this article, we briefly review the pathophysiology and pertinent signals associated with food intake, the recently approved pharmacological treatments for obesity, and several novel treatments currently under investigation.

Methods

This narrative review was performed utilizing targeted literature search of PubMed, MEDLINE, and Google Scholar searches and recent high-impact reviews.[38,39] We began our narrative review by reviewing the included references and searching the above registries with pertinent keywords including obesity, pharmacotherapy, phentermine, naltrexone, bupropion, topiramate, GLP-1, bariatric, anti-obesity, weight loss, and nutrition among others. Included studies were available up to February 1st, 2025. References from retrieved articles were also evaluated to extract relevant studies. Active obesity trials were identified through Clinicaltrials.gov.

Regulation of Appetite

The details regarding the physiology of appetite and caloric consumption have been well described.[40,41] However, a brief review is essential to understanding the mechanism of action of novel pharmacologic treatments of obesity.

Food intake is mainly regulated by a homeostatic and a hedonic process. The homeostatic food intake regulation has three phases: hunger, satiation, and postprandial satiety. These three homeostatic phases drive food intake or appetite behavior of seek, consume, and rest. The hypothalamic arcuate nucleus (ARC) contains orexigenic neurons secreting

Table 1 Definitions of Obesity and Processes of Measuring Obesity

Direct Adiposity Measurements		
Measurement	**Diagnostic Criteria for Obesity**	**Notes**
Dual X-ray Imaging (DXA)	Measures percentage of body fat, Body fat ≥25% in men and ≥30% in women.[7]	Since it generates a 2-dimensional image, cannot measure visceral or ectopic fat well.[8]
CT	Various thresholds capable of diagnosing visceral adiposity.	Radiation Exposure. Capable of accurately evaluating ectopic fat.
MRI	Various thresholds that can provide information about visceral fat area.[9]	No radiation. Time-consuming. Can provide detailed information about adipose tissue breakdown.[10]
Indirect Adiposity Measurements		
Measurement	**Diagnostic Criteria for Obesity**	**Notes**
World Health Organization (WHO) Criteria		
Weight Category	BMI Range (kg/m^2)	
Underweight	Less than 18.5	
Healthy Weight	18.5 to less than 25	18.5 to <23 in individuals of Asian descent.
Overweight	25 to less than 30	23 to <27.5 in individuals of Asian descent.
Class 1 Obesity	30 to less than 35	27.5 to <35 in individuals of Asian descent.
Class 2 Obesity	35 to less than 40	
Class 3 Obesity (severe obesity)	40 or greater	
Waist Circumference – Defining abdominal obesity	Greater than 102 cm (men) or 88 cm (women)	More reliable in men than in women
Waist to Hip Ratio (WHR) - defining abdominal obesity	WHR≥ 0.85 in women and ≥ 0.9- in men	
Sagittal Abdominal Diameter (SAD)	SAD ≥ 25 cm associated with abdominal obesity[11]	Strongest association with visceral adiposity irrespective of age, sex, and degree of obesity[12]
Body impedance assessment	Measures percentage of body fat, Body fat ≥30% in men and ≥42% in women[13]	Less reliable in morbid obesity.[14]

neuropeptide Y (NPY) and agouti-related peptide (AgRP) which increase appetite[38,42,43] (Figure 2A). Additional hypothalamic pathways contributing to hunger involve the lateral hypothalamus and the parabrachial nucleus via calcitonin gene-related peptide (CGRP) neurons.[44,45]

With food entry into the stomach, afferents in the vagus nerve signals to the nucleus tractus solitarius (NTS), and reflexively induces gastric accommodation.[46] This relaxation (Figure 2B) results in distention of the stomach and vagal signals fire to induce the sensation of fullness and terminate the meal. This phenomenon is known as satiation, and individuals perceive this as a sensation of fullness and freedom from hunger.

As food is digested, incretin signals and other enzymes or hormones are released, leading to a fasting state called satiety. The signals start with changes in gastric distention, leading to decreased acyl-ghrelin, increased deacyl-ghrelin, and increased gastric leptin.[47] As food enters the duodenum, other enzymes or hormones including enterokinase, cholecystokinin (CCK), glucose-dependent insulinotropic peptide (GIP, previously called gastric inhibitory polypeptide) and glucagon are all secreted and act systemically to promote postprandial satiety (Figure 2C).[48] With food entry into the small intestine, intestinal L-cells release glucagon-like peptide 1 (GLP-1), which has wide ranging systemic effects promoting satiety.[49–51] Once food reaches the terminal ileum, enterocytes release peptide YY (PYY), oxyntomodulin and

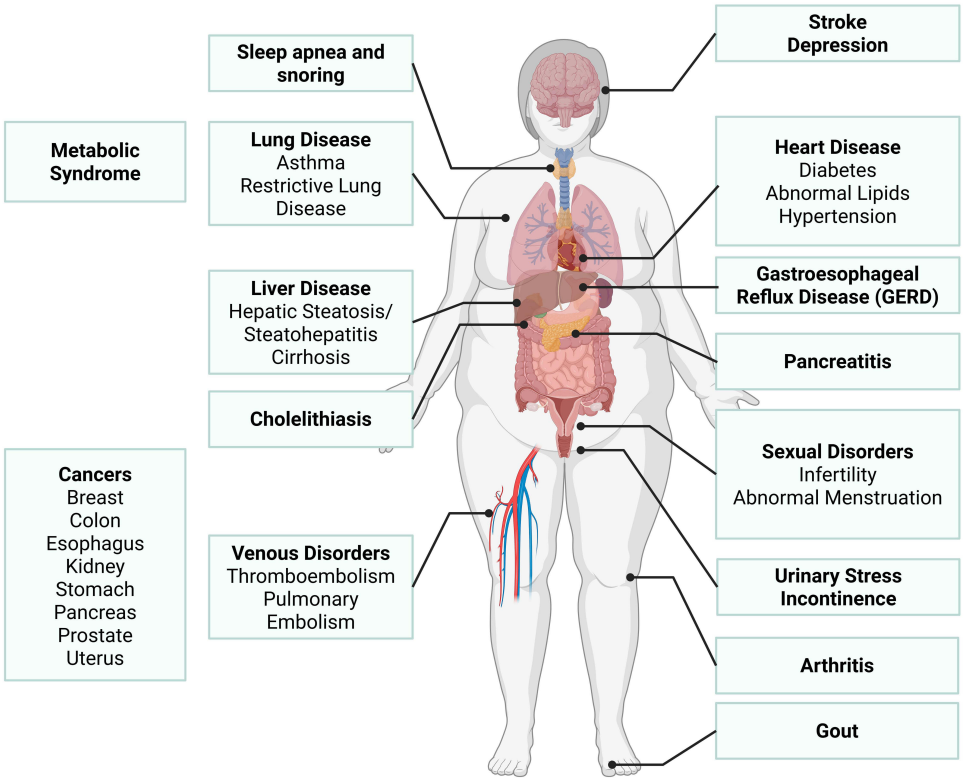


Figure 1 Complications of obesity. Created in BioRender. Fredrick, T. (2025) https://BioRender.com/or5mfyt.

insulin-like peptide 5 (INSL5), which constitute the "ileal brake" and further delay gastric emptying and enteric motility.[52] The cumulative effect is a central sensation of postprandial satiety, (Figure 2C). As food leaves of the stomach, the anorexigenic signaling is reduced, and orexigenic signals from the hypothalamus start to promote hunger, driving the cycle again.

Adipose tissue secretes the hormone leptin, which promotes satiety. After years of excessive intake, adipose tissue stores increase throughout the body, with significant deposition in subcutaneous, liver, and mesenteric tissues. Obesity leads to changes in adipose tissue signaling through upregulation of pro-inflammatory cytokines and induces increased insulin resistance.[53,54]

Regulation of this neurohormonal signaling forms the basis for novel pharmacologic treatments for obesity and obesity-related conditions. When describing the beneficial and adverse effects of each anti-obesity medication, we will highlight the novel mechanisms behind their induction of weight loss.

Pharmacologic Treatments for Obesity

Details of FDA-approved anti-obesity medications are described in Tables 2 and 3, and medications in development are highlighted in Table 4. We will classify pharmacologic treatments based on their mechanisms of action and explicitly characterize those treatments which are approved by the US Food and Drug Administration (FDA) for treatment of obesity.

Anti-Absorptive Treatments

Orlistat

Orlistat was approved by the FDA in 1999 for treatment of obesity in adults.[86] Orlistat inhibits gastric and pancreatic lipase, preventing triglycerides from being hydrolyzed and decreasing the absorption of free fatty acids from the diet. Weight reduction (denoted henceforth with the minus [-] sign) ranges from −2.8 to −4.8% total body weight loss (TBWL).[55,56,70,87] Additional benefits of orlistat include reduced total cholesterol, LDL, fasting glucose, and systolic and diastolic blood pressure

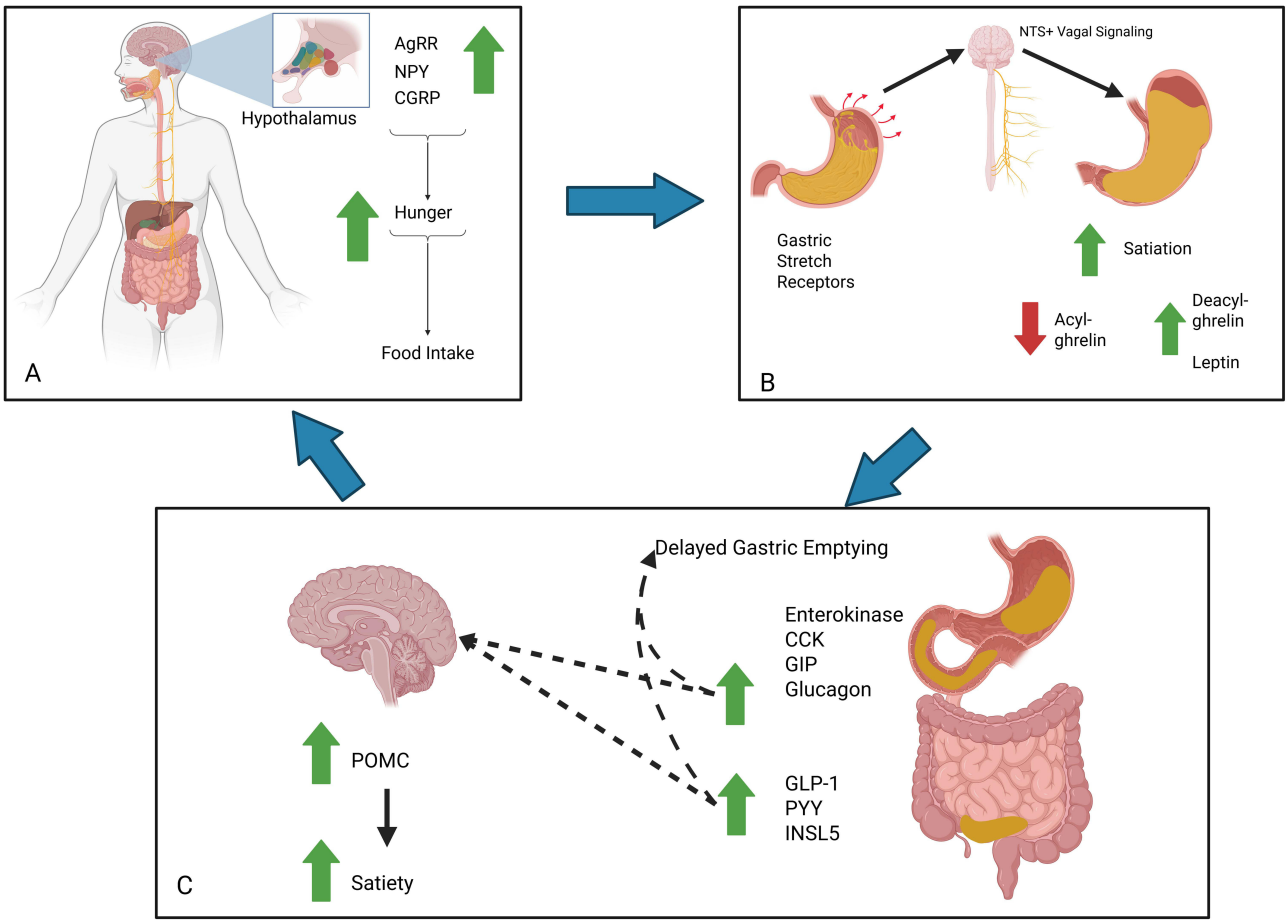


Figure 2 Mechanisms of Hunger, Satiety, and Satiation. (**A**) In the fasting state, hunger arises starting with increased signaling arising from hypothalamic hormones Agouti-related peptide (AgRP), Neuropeptide Y (NPY), and Calcitonin-Gene Related Peptide (CGRP). These hormones contribute to the hunger sensation, which causes individuals to consume food. Upon food entry to the stomach (**B**), the stomach expands, which signals the nucleus tractus solitarius (NTS) in the brainstem. Nerve fibers then signal the stomach fundus to relax and accommodate more food. Changes in gastric hormones, including increased leptin and deacyl-ghrelin and decreased acyl-ghrelin promote changes in satiety (green arrow). As food enters the duodenum (**C**), enterocytes secrete additional hormones, enterokinase, CCK, GIP, and glucagon which both slow gastric emptying and promote satiety. As the bolus reached the ileum, PYY, GLP-1, and INSL5 hormones are secreted and further delay gastric emptying. The end result of these hormones is action at the level of the hypothalamus to increase POMC secretion and promote satiety. Upward green arrows reflect increases, and downward red arrow reflects decreases. Created in BioRender. Fredrick, T. (2025) https://BioRender.com/ gd6ph92.

(Table 5).[88–90] Side effects arise from the reduced fat absorption, including flatulence, fecal urgency, fecal incontinence, and fat-soluble vitamin deficiencies, which result in high rates of treatment discontinuation, and low clinical use.[87,91]

Centrally Acting Medications

Phentermine

Phentermine is a sympathomimetic medication with amphetamine-like stimulant effects initially FDA approved in 1959 for short-term weight loss.[112] Through increasing extracellular dopamine, norepinephrine, and serotonin in the brain, it reduces appetite.[113,114] Side effects arising from the sympathomimetic nature of phentermine include insomnia, palpitations, elevated blood pressure, and gastrointestinal distress.[115] Phentermine is contraindicated in individuals with underlying cardiovascular disease given risk of arrythmias.[116]

Weight loss with phentermine varies from −6.7 to −8.1 kg after 12 weeks of treatment.[71,117] While phentermine is only approved by FDA for 12 weeks use for weight loss, treatment can be continued longer via either continuous or intermittent use, with no increased cardiovascular risk.[58]

Phentermine-Topiramate (Phen-Top)

Topiramate is an anticonvulsant and anti-migraine treatment that induces weight loss of −6 to −8 kg,[118] through unclear

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Table 2 Details on FDA Approved Medications for Weight Loss

Medication	Mechanism of Action	Formulation and Maximum Dosing	Weight Loss Efficacy	Common Adverse Events
Orlistat	Inhibits pancreatic lipase	120 mg orally, 3 times daily for each meal with fat	2.8–4.8% body weight loss relative to placebo at 52 weeks[55–57]	Steatorrhea (20%), abdominal pain (40%), defecation urgency (22–38%)
Phentermine	Increased adrenergic signaling in the CNS	Oral, can be given up to 37.5 mg daily for maximum of 12 weeks	7-8.3% body weight loss at 12 months.[58]	Increased blood pressure, tachycardia, prolonged QT interval, ventricular arrythmias, CNS agitation
Phentermine-Topiramate	Increased adrenergic signaling in CNS (phentermine); unknown mechanism of topiramate, but potentially changes in glutamate neurotransmission	Orally, can be given to a maximum of phentermine 15mg/topiramate 92 mg	9.8–10.9% body weight loss at 12 months.[59,60]	Paresthesias (4–20%), Xerostomia (7–19%), Constipation (8–16%), Upper Respiratory Infection (12–16%)
Naltrexone-Bupropion	Opioid antagonist and dopaminergic and noradrenergic effects on POMC	Oral daily medication, up to a maximum of naltrexone 32 mg/ bupropion 360 mg per day	6.1–9.3% total body weight loss.[61,62]	Nausea (32%), constipation (19%), headache (17%), vomiting (10%), dizziness (9%)
Liraglutide	GLP-1 Receptor Agonist	Subcutaneous (SC) injection up to 3 mg once daily	6-8% body weight loss at 12 months.[63,64]	Nausea (39–42%), vomiting (34%), headache 9–13%), diarrhea (10–22%), constipation (4–19%)
Semaglutide	GLP-1 Receptor Agonist	Subcutaneous (SC) injection up to 2.4 mg weekly	10.76–14.9% total body weight loss at 52 weeks.[65,66]	Nausea (42–44%), vomiting (24–36%), headache (14–17%), diarrhea 8–10%), constipation6-24%), abdominal pain (15–20%)
Tirzepatide	GLP-1 and GIP receptor co-agonist	Weekly subcutaneous injection up to 15 mg weekly.	13.9–17.5% total body weight loss at 52 weeks, and up to 18.4% at 72 weeks.[67–69]	Nausea (12–29%), vomiting (5–14%), diarrhea 12–23%), constipation (6–17%), abdominal pain (5–10%)

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Table 3 Pivotal Trials Results

Medication	Pivotal Trials	Weight Loss Observed in Trial	Additional Health Benefits
Orlistat	Xendos[70]	• Mean weight loss at 4 years: 5.8 kg with orlistat vs 3.0 kg with placebo • 52% completion rate with orlistat vs 34% with placebo	• 37.3% reduction in risk of developing type 2 diabetes • Cumulative diabetes incidence: 6.2% with orlistat vs 9.0% with placebo
Phentermine	Kang et al 2010[71] Lewis et al 2019[58]	Kang 2010 (12 weeks): • Mean weight loss: 8.1 kg with phentermine vs 1.7 kg with placebo • ≥5% weight loss: 95.8% vs 20.8%; ≥10% weight loss: 62.5% vs 4.7% Lewis 2019 (observational): • Continuous use >12 months: 7.4% more weight loss at 24 months vs ≤3 months use	Kang 2010: • Significant improvements in total cholesterol and LDL-C • Improved waist circumference reduction Lewis 2019: • No increased risk of cardiovascular disease or death with longer-term use
Phentermine-Topiramate	Equip, Conquer, Sequel[59,60,72]	EQUIP (56 weeks): • 10.9% weight loss vs 1.6% in placebo CONQUER (56 weeks): • 9.8% weight loss vs 1.2% in placebo SEQUEL (108 weeks): • 10.5% weight loss vs 1.8% in plabeo	• Significant improvements in waist circumference, blood pressure, fasting glucose • Improved lipid profiles (triglycerides, total cholesterol, LDL, HDL) • Decreased rates of incident diabetes
Naltrexone-Bupropion	COR-I, COR-II,[61,73]	COR-I (56 weeks): • 6.1% weight loss vs 1.3% in placebo COR-II (56 weeks): • 6.4% weight loss vs 1.2% in placebo weight loss • ≥5% weight loss: 50.5% vs 17.1%	• Improvements in cardiometabolic risk markers • Improved weight-related quality of life • Better control of eating • Small reduction in blood pressure (~1 mm Hg) • No increased depression or suicidality
Liraglutide	SCALE (Diabetes Mellitus) SCALE Obesity[63,64]	SCALE Diabetes (56 weeks): • 6.0% (6.4 kg) weight loss vs 2.0% (2.2 kg) in placebo Scale Obesity (56 weeks): • 8.4 kg weight loss vs 2.8 kg in placebo • >10% weight loss: 33.1% vs 10.6%	• Improved glycemic control in diabetes patients • Improved metabolic parameters (triglycerides, cholesterol) • Reduction in prediabetes progression • Improvements in blood pressure and lipid profiles
Semaglutide	STEP 1–5 trials.[65,74,75]	STEP 1 (68 weeks): • 14.9% weight vs 2.4% in placebo STEP 5 (104 weeks): • 15.2% weight loss vs 2.6% in placebo STEP 8 vs Liraglutide (68 weeks): • 15.8% weigh loss vs 6.4% in liraglutide	• Improvements in waist circumference • Reduced systolic blood pressure (3.9 mm Hg) • Improved physical functioning scores • Superior to liraglutide for weight loss • Sustained weight loss with continued treatment
Tirzepatide	SURMOUNT and SURPASS[67–69,76]	SURMOUNT-1 (72 weeks): • 15 mg: 20.9% weight loss vs 3.1% with placebo • ≥20% weight loss: 57% (15 mg) vs 3% SURMOUNT-2 (T2D, 72 weeks): • 15 mg: 14.7% weight loss vs 3.2% in placebo SURMOUNT-3 (after lifestyle): • Additional 18.4% weight loss • 87.5% achieved ≥5% additional loss	• Improvements in all cardiometabolic measures • In T2D: Mean HbA1c reduction of 2.34% (15 mg) • Significant improvements in blood pressure, lipids • Effective even after initial lifestyle intervention success

Table 4 Selected Anti-Obesity Medications Under Development

Medication	Mechanism of Action	Current Status	Weight Loss Efficacy
Peripheral Tissue Actors			
Bimagrumab	Anti activin type II receptor (ActRII) monoclonal antibody	Phase 2 trials ongoing	Reduced fat mass by −7.9% relative to placebo at 10 weeks.[77]
Oral GLP-1 Receptor Agonists			
Danuglipron	Daily oral small-molecule GLP-1 RA	Phase 2 trials ongoing	TBWL: −8% to −13% after 32 weeks (NCT04707313).
Orforglipron	Daily oral small-molecule GLP-1 RA	Phase 3 trials ongoing	TWBL: −14.7% vs −2.3% placebo at 36 weeks[78]
Rybelsus (semaglutide)	Daily oral peptide GLP-1 RA	Approved in Diabetes Mellitus, Phase 3 trials in obesity ongoing	TBWL: −15.1% vs −2.4% in placebo at 68 weeks[79]
Subcutaneous (SQ) GLP-1 Receptor Agonists			
Ecnoglutide (XW03)	Weekly SQ GLP-1 RA	Phase 3 trials ongoing	TBWL: −14.7% TBWL at 26 weeks[80]
GZR18	Bi-weekly SQ GLP-1 RA	Phase 2 trials completed	–17.29% TBWL at 30 weeks (CTR20231695)
GLP-1/ Glucagon Receptor (GCG) Dual Agonists			
Mazdutide	Weekly SQ GLP-1/GCG dual agonist	Phase 2 trials completed	−11.3% vs 1% in placebo at 24 weeks.[81]
Pemvidutide	Weekly SQ GLP-1/GCG dual agonist	Phase 3 trials ongoing	−15.6% TBWL vs placebo at week 48[82]
Survodutide	Weekly SQ GLP-1/GCG dual agonist	Undergoing Phase 3 trials	−14.9% weight loss vs −2.8% weight loss in placebo at 46 weeks
GLP-1 and GIP Receptor Agonists			
Maridebart cafraglutide (AMG 133/MariTide)	Weekly SQ GLP-1/GIP dual agonist	Phase 2 trials completed	−20% weight loss at 52 weeks[83]
GLP-1, GIP, GCG Receptor Agonists			
Retatrutide	Weekly SQ GLP-1/GCG/GIP Triple Agonist	Undergoing Phase 3 trials	−24.2% weight loss vs −2.1% in placebo at 48 weeks[84]
GLP-1 and Amylin Receptor Agonists			
Cagrisema (cagrilintide and semaglutide)	Weekly subcutaneous injection of GLP-1 and Amylin dual agonist	Undergoing phase 3 trials	−12.6% weight loss at 32 weeks.[85]

mechanisms, but likely by modulating GABA in the hypothalamus.[119] Combination 15 mg/92 mg phentermine-topiramate resulted in −10.92% weight loss vs −1.55% in placebo at 56 weeks,[59] and was confirmed in patients followed up to 108 weeks.[60,72]

Secondary benefits include a weight-loss mediated reduction in blood pressure, reduced triglycerides and LDL, improved fasting glucose, fasting insulin, and high-sensitivity C-reactive protein (HS-CRP).[60] In a small randomized controlled trial (RCT), followed by a pragmatic trial, phentermine-topiramate was shown to work best in those with abnormal satiation, defined as need for high calorie intake to reach fullness.[33,120]

Table 5 Additional Benefits of FDA-Approved Anti-Obesity Treatments. Summary of Potential Additional Benefits From AOM Which Have Previously Been Investigated

Medication	Steatohepatitis	Liver Fibrosis	Kidney Disease	Cardiovascular MACE (in diabetes)	Cardiovascular MACE (in obesity)	Heart Failure	Sleep Apnea	Arthritis	Stroke	Infertility
Orlistat	?	?	?	N/A	?[92,93]	?[93]	?	?	?[93-94]	?
Phentermine-Topiramate	?	?	?	N/A	?[95]	?	?	?	?	?
Naltrexone-Bupropion	?[96]	?	?	N/A	X[73]	X[73]	?	?	?	?
Liraglutide	+[97]	-[97]	+[98]	+[99]	?	?	[100-101]	?	?	?
Semaglutide	+[102]	-[102]	+[103]	+[99]	[104]	? [105]	?	[106]	?	?
Tirzepatide	+[107]	-[107]	+[108]	+[109]	?	+[110]	+[111]	?	?	?

Notes: + = High quality evidence that this medication can clinically improve the listed condition. ? = Further investigations are needed. - = Adequate evidence that AOM does not promote either enough weight loss or improve clinical parameters enough to improve outcome.

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Naltrexone-Bupropion (NB)

Bupropion increases hypothalamic dopamine and norepinephrine signaling, reducing food intake,[121–124] and naltrexone is approved for opioid abuse and helps reduce cravings for alcohol. The combination therapy naltrexone-bupropion (NB) has been shown to result in TBWL up to −6.1% compared to −1.3% in the placebo group at 56 weeks.[61,73] When combined with intensive lifestyle changes, NB weight loss was −9.3% compared to −5.1% with placebo.[62] The most common adverse events with NB include nausea, headache, constipation, dizziness, vomiting, and dry mouth. NB improves central obesity and LDL levels but without significant improvement in other cardiovascular parameters.[61,62,73,125] NB is effective in binge eating disorder, which presents a patient population potentially best served by this medication.[126]

Setmelanotide

Setmelanotide is a daily subcutaneous injection which acts as a melanocortin-4 (MC4) receptor agonist, and was approved by the FDA in 2020 in patients with obesity arising from genetically confirmed Bardet-Biedl syndrome (BBS), POMC, PCSK1, or LEPR deficiency.[127,128] Human studies of setmelanotide showed significant weight loss and improved hunger scores.[129] A phase 2 study of 18 patients with hypothalamic obesity found that setmelanotide led to 80% experiencing ≥ 5% body weight loss at 16 weeks.[130] Adverse events of setmelanotide include nausea, depression, suicidal ideation, and hyperpigmentation.[127,129–131] Its use remains limited for these genetic alterations in MC4R signaling and given its specific actions is unlikely to be effective in the general population.

Incretin Agonists

GLP-1 Receptor Agonists

One class of anti-obesity medications experiencing a large rise in prescriptions are the GLP-1 receptor agonists (GLP-1RAs, Figure 3). GLP-1 RAs have been shown to impact functions associated with metabolism and energy balance by delaying gastric emptying, reducing hunger, increasing postprandial satiety, and reducing ad libitum food intake.[132–134] In addition, GLP-1 activation in the CNS via the hypothalamus and medulla drives reduced appetite.[135–137] GLP-1 directly acts on pancreatic B-cells to increase insulin secretion and on hepatic cells to decrease glucagon excretion and regulate blood glucose levels, leading to reductions in body fat.[138–140]

Liraglutide

Liraglutide was developed by modifying GLP-1 protein to include a free fatty acid side chain bound to the peptide, allowing for albumin binding and (longer) half- allowing for daily dosing.[142] Five randomized controlled trials of liraglutide in individuals with obesity have shown weight loss of −4.4 kg to −6.1 kg relative to placebo.[63,64,143–145]

Semaglutide

Semaglutide is a GLP-1 RA with significantly longer half-life supporting weekly SQ administration. Like liraglutide, the GLP-1 sequence of semaglutide is bound to a free fatty acid side chain, mediating even stronger coupling to albumin.[146,147]

The STEP trials were the pivotal trials evaluating semaglutide for obesity.[65] The STEP 1 randomized controlled trial investigated semaglutide 2.4 mg weekly and found a body weight loss of −14.9% vs −2.4% with placebo at 68 weeks.[148] Similar effects were seen across STEP 2–5 and STEP 8 (which included both overweight and obese without diabetes), with sustained weight loss seen at 104 weeks in the STEP 5 trial.[149,150]

Additional benefits of semaglutide include reduced incidence of cardiovascular complications in individuals with type 2 diabetes and chronic kidney disease.[151,152] The SELECT RCT showed improvement in a composite endpoint of death from cardiovascular causes, nonfatal MI, or nonfatal stroke in individuals receiving semaglutide relative to placebo (HR=0.80, 95% CI 0.72–0.90).[152] Pooling results from additional trials including SELECT, FLOW, STEP-HFpEF, and STEP-HFpEF DM confirmed improvement in composite outcomes in patients with heart failure (HF) with preserved ejection fraction, but no significant reduction in cardiovascular death alone in individuals receiving semaglutide.[105] Notably, these studies included variable dosages of semaglutide, with few individuals on the maximum dosage used for obesity treatment. Recommendations from the American College of Cardiology have yet to support empiric GLP-1 RA use for HF.[153,154]

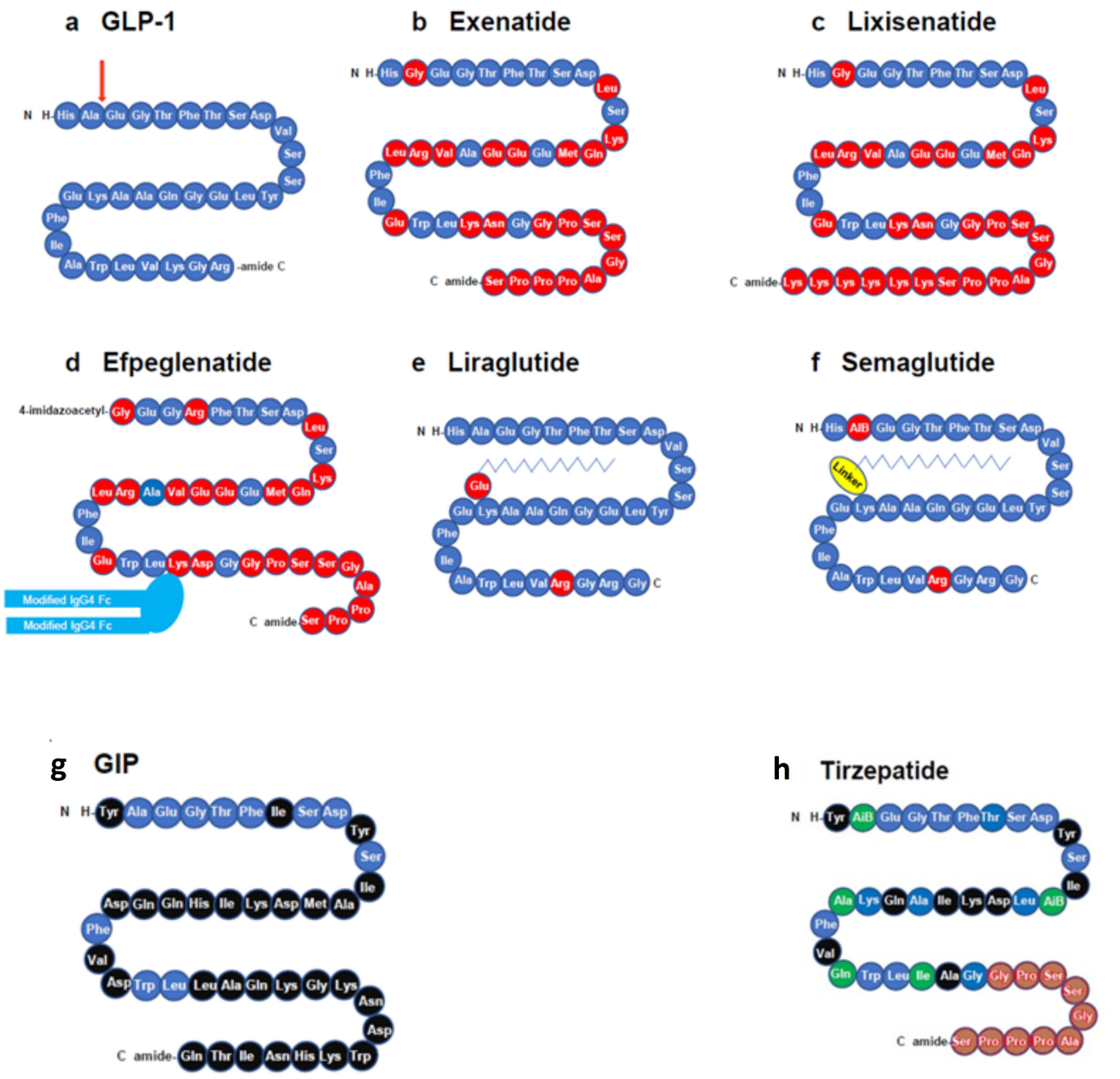

Figure 3 Composition of Different Incretin Agonists. Structures of formulations of GLP-1 receptor agonists (**a**) GLP-1, (**b**) exenatide, (**c**) lixisenatide, (**d**) efpeglenatide, (**e**) liraglutide, (**f**) semaglutide, (**g**) GIP and (**h**) tirzepatide. Amino acids are illustrated in circles; red circles show amino acids that are different from those in GLP-1; blue circles show amino acids that are identical to those in GLP-1; black circles show amino acids that are present in GIP and tirzepatide but not in GLP-1; brown circles show amino acids that are identical in tirzepatide and exenatide, and green circles show amino acids that are present in tirzepatide but not in GLP-1, GIP or exenatide. AiB, aminoisobutyric acid. The red arrow in (**a**) illustrates the site of DPP-4 inactivation. Adapted from Tschöp M, Nogueiras R, Ahrén B. Gut hormone-based pharmacology: novel formulations and future possibilities for metabolic disease therapy. *Diabetologia*. 2023/10/01 2023;66(10):1796–1808. Creative Commons.[141]

Secondary benefits of GLP-1 receptor agonists and other anti-obesity medications remain an active area of investigation and are summarized in Table 5. These include improvement in MASLD-related steatohepatitis and steatosis,[155,156] knee pain in osteoarthritis,[106] cardiovascular outcomes,[99] and potentially substance use disorders.[157]

Common side effects of GLP-1 agonists include nausea, constipation, diarrhea, vomiting, abdominal discomfort, and reduced appetite.[63,67,148,158] Side effects tend to be transient and resolve with time, but impact real-world adherence.[159] Patients on GLP-1 receptor agonists do lose muscle mass, as is commonly seen with all forms of weight loss.[160] Serious adverse events include gallbladder and biliary disease, which are believed to be dose-related and result from GLP-1 inhibiting gallbladder emptying through CCK suppression.[120,140] Contraindications to use of GLP-1 receptor agonists

include medullary thyroid carcinoma, family history of MEN type 2 syndrome, pancreatitis, and relative contraindications include diabetic retinopathy and uncontrolled diabetes.[161,162]

Given the recent approvals of these anti-obesity medications, providers and patients are undoubtedly concerned about what long-term safety data is available. Human studies have shown these medications are safe, and even protective when patients are followed for up to 5 years.[163]

GIP

GIP acts in synergy with GLP-1 to regulate postprandial insulin secretion.[164] The effect of GIP agonism in obesity is most significant when combined with GLP-1 agonism. GIP-induced inhibition of centrally mediated emesis signals triggered by GLP-1 administration enhances weight loss seen with GLP-1 RA administration.[165] Unlike GLP-1, GIP by itself does not retard gastric emptying.[166]

Tirzepatide

The GLP-1/GIP co-agonist, tirzepatide, has shown efficacy for both management of diabetes mellitus and weight loss.[167] The SURMOUNT-1 trial found mean 72-week weight loss up to −20.9% at 15 mg weekly compared to −3.1% with placebo.[67] Similar results were seen in the 5 SURPASS trials.[76,168–171]

Tirzepatide was approved by the FDA for weight loss in 2022.[172,173] Significant benefits for obesity-associated diseases are also being reported (Table 5) including reduced heart failure events at 104 weeks of follow up (hazard ratio [HR] 0.62 compared to placebo),[110] improved management of obstructive sleep apnea at 52 weeks,[111] and improved management of metabolic-dysfunction associated steatohepatitis (MASH) with a decrease of ≥1 fibrosis stage with no worsening of MASH at 52 weeks.[107] Side effects of tirzepatide are similar to those of the GLP-1 receptor agonists.[169,172,173]

Real-World Impacts

Although weight loss is significant in clinical trials of these medications, real-world evidence has shown significant variability in weight loss.[174] Given high costs of these medications, discontinuation rates are as high as 50%, resulting in most real-world studies showing weight loss lower than clinical trials.[174] Desire for these medications led to high levels of compounded formulations, potentially representing increased safety events reported in adverse events reported in Europe.[175]

AOMs Under Investigation

With advances in understanding of the incretin system, there has been substantial development of new agents for obesity. Currently there are over 100 agents being investigated in human trials.[176] While each potential agent is beyond the scope of this review, we will focus on selected compounds anticipated for phase 3 trials, grouped by their mechanism of action and detailed in Table 4.

Peripheral Tissue Actors

Bimagrumab

Bimagrumab is a human monoclonal antibody that binds to the activin type II receptor (ActRII), which inhibits ligands which negatively regulate skeletal muscle growth.[177] A single dose of bimagrumab increased lean mass by 2.7% and reduced fat mass by −7.9% at 10 weeks relative to placebo, and improved markers of insulin sensitivity.[178] Bimagrumab also led to significant reductions in fat mass, waist circumference, improved lean mass, and reduced hemoglobin A1C. Side effects include respiratory tract infections (in elderly), rashes, and diarrhea, and muscle spasms.[177]

Additional GLP-1 RAs

Oral formulations of GLP-1 RAs with absorption enhancers have been developed, with semaglutide (Rybelsus) currently approved for management of diabetes mellitus.[156] To investigate weight loss, the OASIS trials pursued higher doses of up to 50 mg daily, which led to up to −15.1% body weight loss vs −2.4% in placebo.[179]

Orforglipron is a non-peptide oral GLP-1 RA which has completed phase 2 trials and has shown weight reduction ranging from −8.6% to −12.6% along with improved hemoglobin A1C.[78,180,181] Danuglipron represents another non-peptide oral GLP-1 RA shown to lead to −8% to −13% weight loss after 32 weeks of treatment.[182]

Novel subcutaneous GLP-1 RA competitors are also being investigated. Ecnoglutide (XW03), is in phase 3 trials after phase 2 trials showed up to −14.7% TBWL at 26 weeks (80). GZR18 is a novel GLP-1 injection with bi-weekly dosing in phase 2 trials that has demonstrated up to –17.29% TBWL at 30 weeks (CTR20231695).

Glucagon

Glucagon presents an important target for weight management and metabolism. Excess adiposity causes glucagon resistance, and leads to MASLD by reducing lipid metabolism in the liver.[183] The glucagon receptor (GCGR) also plays a key role in thermogenesis, or the burning of calories.[184] Thus, changes in the incretin signaling process can drive changes in body composition.

Several GLP-1 and glucagon receptor (GCGR) co-agonists are in development. Phase 3 trials of Mazdutide showed −14.0% TBWL vs 0.3% body weight gain in placebo group at 48 weeks.[185] Survodutide has also demonstrated an average TBWL of −14.9% vs −2.8% on placebo after 46 weeks.[186] Treatment was also associated with improvement in MASH with no worsening of fibrosis after 48 weeks treatment.[187] Phase 3 trials are ongoing to assess survodutide for obesity and MASH.[188]

Triple Agonism

Given the additive effect of GCGR agonism to GLP-1 agonism, combining these with GIP agonism presented a novel therapeutic target. One "triple agonist" to GLP-1/GIP/GCGR, retatrutide, is a single peptide conjugated to a fatty diacid moiety that showed a mean TWBL in obesity of −24.2% vs −2.1% in placebo after 48 weeks,[84] with significant reductions in liver fat after 24 weeks.[189] Adverse events were frequent and most commonly GI related. Phase 3 trials for obesity, diabetes mellitus, and cardiovascular outcomes are currently ongoing.

Amylin

Pramlintide is a synthetic amylin analog approved for management of diabetes with only modest weight loss.[190] Cagrilintide is a long-acting amylin analog administered once-weekly. Phase 2 trials of the combination of cagrilintide and semaglutide (CagriSema) have shown a synergistic effect on TWBL, showing −15.6% in combined treatment vs −5.1% in semaglutide only after 32 weeks.[85]

Comparisons of Different Anti-Obesity Medications

Few studies have evaluated the medications detailed above in head-to-head comparisons, which remains an area of investigation. The STEP-8 RCT found greater weight loss with semaglutide than with liraglutide at 68 weeks (Table 3).[74]

Comparisons of tirzepatide to semaglutide head-to-head remain limited to few studies.[169,191,192] However, both the randomized clinical trial of Frias et al from 2021[169] and the Bayesian meta-analysis of Ding et al from 2024[191] did not evaluate the maximum dose of semaglutide, but rather the 1 mg weekly dosing. Results from the SURMOUNT-5 RCT are anticipated to be available this year and will reflect a direct comparison of tirzepatide 15 mg and semaglutide 2.4 mg weekly.[193]

One head-to-head trial compared orlistat to liraglutide at up to 1 year and found that patients on liraglutide lost −3.8 kg more than those on orlistat.[144]

Treatment Adjuncts to Pharmacological Agents in Obesity

A proposed framework for treating obesity is outlined in Figure 4. When starting individuals on anti-obesity treatment, we recommend first starting to ascertain the reasons for which individuals are obese. Readily reversible causes and causative medications should be evaluated and addressed.[194] All patients benefit from dietary and lifestyle modification:[66] reducing caloric intake to 1200–1500 or 1500–1800 calories per day for women and men respectively,[195] with incorporation of moderate-intensity exercise of 150 minutes per week.[196] Administration of anti-obesity medications alone, without incorporating lifestyle treatments limits effectiveness and fails to provide the lifelong changes needed to promote weight maintenance.[197] Failing to address the role of dietary changes and exercise adoption when treating obesity would not be within the ethical guidelines of most societies. Medications are not without side effects, and providers must always weigh potential risks and benefits prior to prescription.[198]

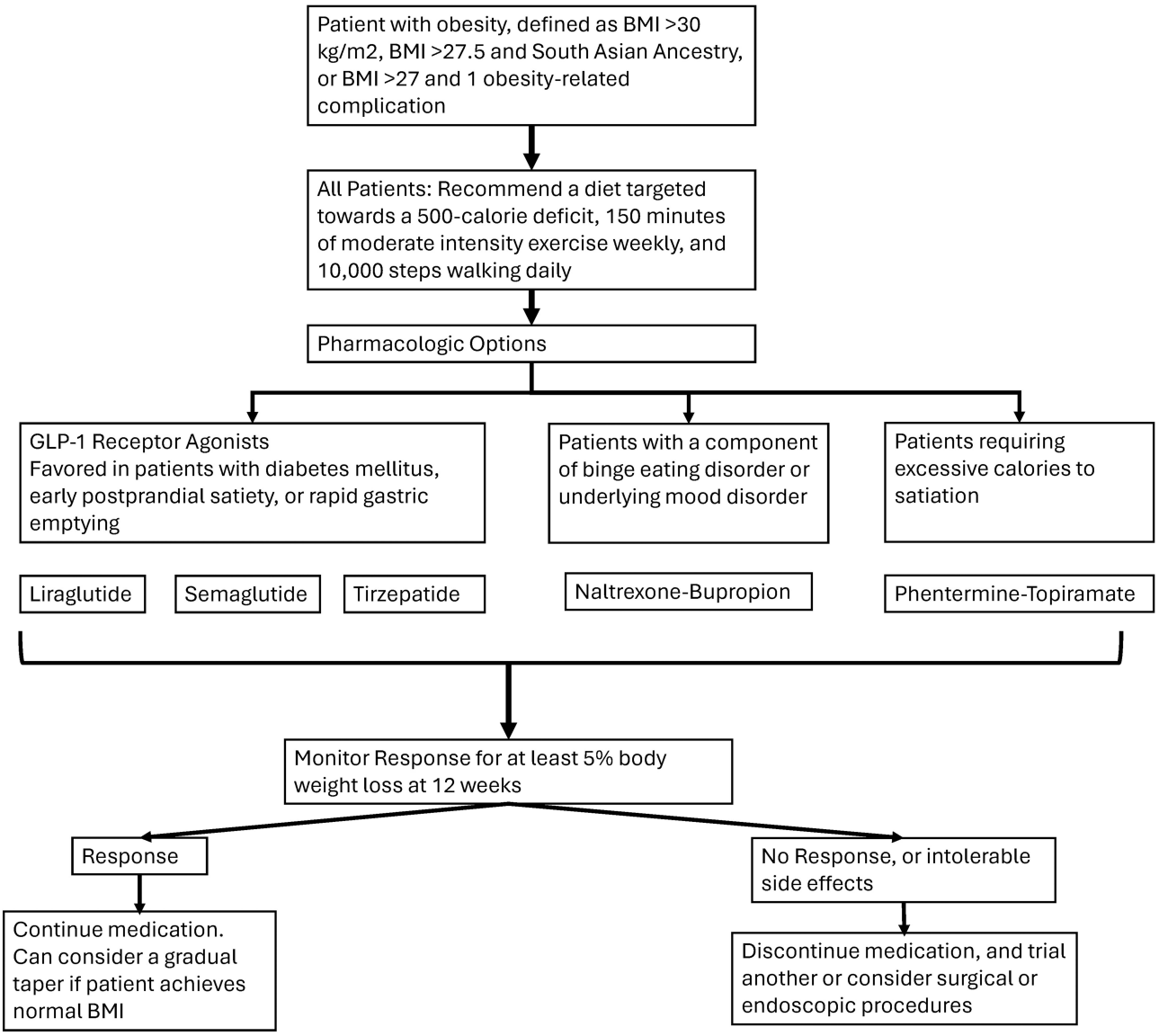

Figure 4 A proposed treatment scheme for anti-obesity medications.

Our practice aims to personalize the treatment for obesity to each patient (Figure 4). Certain patients tend to get hungry quickly after meals, or have abnormal postprandial satiety and may benefit from medications that slow gastrointestinal transit such as the GLP-1 RAs.[199] Those with diabetes also benefit greater from GLP-1 RAs and tirzepatide given the positive effects on insulin sensitivity. Patients who require more calories to feel full at any one meal may benefit from the effects on satiation signaling observed with phentermine-topiramate.[200] Individuals with binge-eating traits or anxiety disorders may benefit from NB over other therapies.[120]

Bariatric surgery has been one of the longest-studied treatments for obesity, with up to 25–30% TBWL after Roux-en -Y gastric bypass and 18–20% TBWL after sleeve gastrectomy, and recent research shows that weight regain is associated with increased morbidity and mortality.[31,201] Endoscopic procedures have presented a novel alternative for weight loss, showing up to 15% TBWL at 1 year.[202] The positioning of pharmacologic therapies relative to bariatric and endoscopic procedures remains to be determined.

Assessment of Pharmacologic Response to Selected Strategies

It is important to evaluate treatment response shortly after starting pharmacologic treatment for obesity early to ensure effectiveness. Patients who are likely to demonstrate long-term response to GLP-1 RAs will likely lose a significant amount of weight within the first month.[203–205]

Patients who fail to lose weight on treatment initiation should be evaluated for side effects, cost, or other factors impairing medication adherence. If side effects are unbearable, or they truly do not respond well it is reasonable to pursue a medication with an alternative pharmacological action.[206,207]

One important aspect of GLP-1 RA use is weight regain that occurs with stopping the medication.[75,208,209] Strategies to combat this weight loss include aggressive dietary management, cognitive behavioral therapy, and switching to different anti-obesity medications.[210–212]

When switching from one once-weekly GLP-1 RA to another, it is ideal to stop the current GLP-1 RA, then begin the new GLP-1 RA one week later. It is recommend to restart the new GLP-1 RA at a reduced dose and titrate to the maximum tolerated dose, since side effects are more likely if starting immediately at the higher dose.[213] When switching between GLP-1 RAs, providers should meet with patients within 2–3 months to assess for side effects and monitor for treatment efficacy.

The duration of the use of pharmacological agents including incretin agonists for longer than 68 weeks is not based on clinical trial evidence and requires full discussion between the patient and provider. The risks of weight regain compared to continued incretin agonist use should be evaluated, and dietary and lifestyle modifications should play an instrumental role in preventing weight regain in those who discontinue incretin agonists. Weight loss can also alter pharmacokinetics of many medications, and medication doses may require adjustment in patients receiving these medications.[214]

Economic Analysis of Pharmacotherapy

Many of the newer agents discussed in this review are not without high cost. The cost of novel GLP-1 agonists can be between $10-20,000 annually. Economic analysis comparing different anti-obesity medications has found inconclusive evidence of cost-effectiveness of semaglutide and liraglutide, with some support suggesting phentermine and orlistat are cost-effective.[215] When comparing anti-obesity medications to bariatric surgery, multiple analysis have shown that bariatric surgery is more cost-effective than pharmacologic therapies, particularly the GLP-1 RAs.[216] Additionally, it remains to be determined if reimbursement modules should vary based upon severity of an individual patient's obesity. As further treatments are developed, additional analyses into cost effectiveness are certainly warranted.

Conclusion

The realm of pharmacologic treatments for obesity continues to expand rapidly. With the development of additional incretin agonists, we can expect the range of options for obesity and related comorbidities to improve dramatically. Further investigations are needed to address long-term use of incretin agonists and to provide recommendations for prevention of weight regain.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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