Journal of Obesity & Metabolic Syndrome 2023;32:106-120
https://doi.org/10.7570/jomes23032

jomes
pISSN 2508-6235
eISSN 2508-7576

Review

Approved Anti-Obesity Medications in 2022 KSSO Guidelines and the Promise of Phase 3 Clinical Trials: Anti-Obesity Drugs in the Sky and on the Horizon

Eonju Jeon[1], Ki Young Lee[2,*], Kyoung-Kon Kim[3,*]

[1]Division of Endocrinology and Metabolism, Department of Internal Medicine, Daegu Catholic University School of Medicine, Daegu; [2]Division of Endocrinology and Metabolism, Department of Internal Medicine, [3]Department of Family Medicine, Gachon University College of Medicine, Incheon, Korea

Obesity is a prevalent global health issue affecting approximately half of the world's population. Extensive scientific research highlights the urgent need for effective obesity management to mitigate health risks and prevent complications. While bariatric surgery has proven to be highly effective, providing substantial short-term and long-term weight loss and resolution of obesity-related comorbidities, it is important to recognize its limitations and associated risks. Given the global obesity epidemic and the limitations of surgical interventions, there is high demand for effective and safe anti-obesity medications (AOMs). In Korea, the Korean Society for the Study of Obesity strongly advocates for the use of pharmacotherapy in Korean adults with a body mass index of 25 kg/m^2 or higher who have not achieved weight reduction through non-pharmacological treatments. Currently, five AOMs have been approved for long-term weight management: orlistat, naltrexone/bupropion, phentermine/topiramate, liraglutide, and semaglutide. Tirzepatide is awaiting approval, and combination of semaglutide/cagrilintide and oral semaglutide are currently undergoing rigorous evaluation in phase 3 clinical trials. Furthermore, other promising drugs, including orforglipron, BI 456906, and retartrutide, are progressing to phase 3 studies, expanding the therapeutic options for obesity management. In personalized patient care, physicians play a crucial role in accurately identifying individuals who genuinely require pharmacotherapy and selecting appropriate AOMs based on individual patient characteristics. By integrating evidence-based interventions and considering the unique needs of patients, healthcare professionals significantly contribute to the success of obesity management strategies.

Key words: Anti-obesity agents, Gastrointestinal hormones, Gastric inhibitory polypeptide, Glucagon-like peptide 1, Glucagon, Ligands

Received May 26, 2023
Reviewed June 6, 2023
Accepted June 20, 2023

*Corresponding author
Kyoung-Kon Kim

https://orcid.org/0000-0003-0374-2571

Department of Family Medicine, Gachon University Gil Medical Center, Gachon University College of Medicine, 21 Namdong-daero 774beon-gil, Namdong-gu, Incheon 21565, Korea
Tel: +82-32-458-2778
Fax: +82-32-460-2391
E-mail: zaduplum@aim.com

*Co-Corresponding author
Ki Young Lee

https://orcid.org/0000-0002-0333-7093

Division of Endocrinology and Metabolism, Department of Internal Medicine, Gachon University Gil Medical Center, Gachon University College of Medicine, 21 Namdong-daero 774beon-gil, Namdong-gu, Incheon 21565, Korea
Tel: +82-32-458-2753
Fax: +82-32-460-2381
E-mail: kylee@gilhospital.com

INTRODUCTION

Obesity is a chronic and progressive disease with serious health consequences, but weight loss brings significant improvements in metabolic markers and overall health. Even small amounts of weight loss yield improvements in metabolic markers, with greater benefits observed as weight loss increases. Larger weight reduction leads to substantial improvements across various health measures,

including glycemic control, triglyceride levels, blood pressure, and high density lipoprotein cholesterol.[1] Conditions like sleep apnea, hepatitis, and fertility-related issues require more substantial weight loss for clinical improvements.[1] Greater weight loss also enhances quality of life, mobility, and other factors.[1] Larger weight reduction offers notable advantages in overall health.

Bariatric surgery is known for its effectiveness in achieving significant short-term and long-term weight loss and resolving obesity-related complications. However, it is important to acknowledge the limitations and potential risks associated with the procedure. Early complications may include bowel obstruction, venous thromboembolism, bleeding, anastomotic leak, wound infection, and internal hernia.[2] Late complications can manifest as stricture, cholelithiasis, incisional hernia, and nutritional deficiencies.[2] Additionally, many patients may experience weight regain over time.[3] Considering these factors, it is unrealistic to expect that bariatric surgery will be suitable for the majority of individuals with obesity. There is a need for effective and reversible biologic interventions that can address the drawbacks associated with bariatric surgery.

Pharmacotherapy is beneficial for individuals with obesity and comorbidities who have not achieved sustainable weight loss through lifestyle changes alone. The availability of new generation anti-obesity medications (AOMs) that can result in weight loss exceeding 10% makes this approach particularly relevant. Our review covers the updated obesity pharmacotherapy guidelines recommended by the Korean Society for the Study of Obesity (KSSO), currently available long-term AOMs in Korea, and upcoming and potential future AOMs.

THE UPDATED OBESITY PHARMACOTHERAPY GUIDELINES RECOMMENDED BY KSSO

The most recent version of obesity management guidelines by KSSO was published in 2022.[4] The recommendations regarding obesity pharmacotherapy are as follows:

(1) The basic treatment for obesity is diet therapy, exercise therapy, and behavioral therapy, and it is recommended to use medication as an additional treatment method only in combination with these.

(2) In Korean adults with a body mass index (BMI) of 25 kg/m^2 or more who have failed to lose weight with non-medicinal treatment, pharmacotherapy should be considered.

(3) For long-term weight management, it is recommended to use medications that have been approved based on large-scale clinical trials.

(4) If at least 5% weight loss is not achieved within 3 months of maintenance dosage of AOM, it is recommended to change or stop the medication.

In Korea, currently available AOMs for adults with obesity, long-term weight loss options include orlistat, naltrexone/bupropion (NB) extended-release (ER), liraglutide, and phentermine/topiramate (P/T) ER, semaglutide, while short-term treatment options include phentermine, diethylpropion, phendimetrazine, and mazindol. The AOMs for children and adolescents include phentermine (for those aged ≥ 16) for short-term treatment, and orlistat (for those aged ≥ 12) and liraglutide (for those aged ≥ 12) for long-term treatment.

The globally accepted indications for pharmacotherapy based on BMI are BMI ≥ 30 kg/m^2 or BMI ≥ 27 kg/m^2 with comorbidities.[5,6] Most approved AOMs in Korea adhere to these criteria. Considering Korean racial characteristics, KSSO recommends pharmacotherapy for patients with BMI ≥ 25 kg/m^2 who failed non-pharmacological treatments.[4] When prescribing medications based on non-approved indications, physicians should thoroughly explain the benefits and risks beforehand.

The choice of medication should consider accompanying conditions such as type 2 diabetes mellitus (T2DM), hypertension, coronary artery disease, chronic kidney disease, and liver disease. The efficacy and safety of the five approved long-term medications are supported by large-scale clinical studies, and dosage is determined based on these findings. Individualized dosage adjustments are necessary, considering patient response and adverse events (AEs). If there is no response, discontinuation of medication is recommended due to individual variability and potential AEs. In adults, if a weight loss of > 5% is not achieved within 3 months of maintenance dosage, the medication should be discontinued or changed. In children and adolescents, if there is < 4% decrease in BMI or BMI z-score after 12 weeks of medication, it is considered ineffective and should be changed or discontinued.

CURRENTLY AVAILABLE NON-PEPTIDE AOMs

Orlistat

Orlistat was approved for long-term weight management by the Food and Drug Administration (FDA) in 1999 and the Korea Ministry of Food and Drug Safety (KMFDS) in 2000. To date, orlistat is the only available AOM that does not directly affect the central appetite center. Orlistat, a reversible inhibitor of lipases, exerts its therapeutic activity in the lumen of the stomach and small intestine, by binding covalently to the active serine residue site of gastric and pancreatic lipases.[7] This binding results in the partial inhibition of triglyceride hydrolysis.[7] Undigested triglycerides are excreted through the fecal route.

At the recommended therapeutic dose of 120 mg three times a day, orlistat inhibits approximately 30% of dietary fat absorption. The weight loss effect is dependent on the dosage, so it is advisable to adhere to the recommended dosage. The medication should be taken with a meal or within 1 hour of eating. No dosage adjustment is required for discontinuation or re-administration of the medication.

In the 4-year XENical in the Prevention of Diabetes in Obese Subjects (XENDOS) trial, which is one of the longest trials involving orlistat, 3,305 participants with obesity and either normal or impaired glucose tolerance were randomly assigned to receive either orlistat or placebo along with lifestyle modification.[8] After 1 year, the orlistat group achieved an 11% reduction in body weight compared to 6% in the placebo group. However, over the following 3 years, both groups experienced weight regain. At the end of the 4-year period, the orlistat group had lost 6.9% of their body weight, while the placebo group lost 4.1%. Notably, taking orlistat for 4 years resulted in a 45% reduction in the progression from impaired glucose tolerance to T2DM.

Gastrointestinal AEs, such as stool incontinence, oily stool, and fatty stool, are common with orlistat use, with frequency rates ranging from 15% to 30% in most studies.[9] It is recommended to supplement with multivitamins to compensate for the potential malabsorption of fat-soluble vitamins. In a recent study utilizing nationwide electronic healthcare records from the Clinical Practice Research Datalink, orlistat has been found to be associated with reduced rates of major adverse cardiovascular events, new-onset heart failure, renal failure, and mortality.[10]

Table 1. The effects of approved long-term therapies for obesity compared to placebo on body weight and waist circumference

Variable	Pooled weighted mean difference (95% CI)	
	Body weight (kg)	Waist circumference (cm)
Orlistat 120 mg tid*	–2.60 (–3.04 to –2.16)	–2.3 (–2.8 to –1.7)
Naltrexone/bupropion ER 32/360 mg qd*	–4.95 (–5.94 to –3.96)	–3.5 (–4.4 to –2.6)
Liraglutide 3.0 mg subQ qd*	–5.27 (–6.06 to –4.52)	–4.0 (–5.0 to –3.3)
Phentermine/topiramate ER 15/92 mg qd*	–8.80 (–10.20 to –7.42)	–7.0 (–8.4 to –5.6)
Semaglutide 2.4 mg weekly†	–11.19 (–15.12 to –7.27)	–8.8 (–11.1 to –6.56)

*Pooled weighted mean differences (95% CI) of body weight loss and waist circumference in excess of placebo, obtained from previous meta-analysis reports[11,12]; †Pooled weighted mean difference (95% CI) calculated by conducting meta-analyses using R version 4.3.0 (R Core Team) and the meta package version 6.2-1, with data from STEP 1–6 and 8 trials.[13-19]
CI, confidence interval; tid, three times a day; ER, extended-release; qd, once daily; subQ, subcutaneous.

Orlistat has been a proven drug for over 20 years. While it may be less effective compared to other available drugs (Table 1),[11-19] it has the advantage of being cost-effective and has fewer AEs.[20]

Naltrexone/bupropion extended-release

NB combination was FDA-approved in 2014 and KMFDS approved in 2016 for long-term weight management. Naltrexone is an opioid receptor antagonist used to treat alcohol and opioid dependence. Bupropion is an antidepressant that inhibits dopamine and norepinephrine reuptake inducing weight reduction at 300 to 400 mg/day.[21] While naltrexone alone has minimal weight loss benefit, combining it with bupropion diminishes the μ-opioid receptor autoinhibitory feedback loop in anorexigenic hypothalamic neurons activated by bupropion, leading to additive reduced food intake and weight loss.[22]

The initial dose is one tablet (NB 8/90 mg) taken orally once daily in the morning for 1 week. Over the course of 4 weeks, the dose is increased gradually to the treatment dose of two tablets taken twice daily (total daily dose of NB 32/360 mg).

NB was investigated in four large-scale, randomized, double-blind, placebo-controlled trials that lasted for 1 year. Three of these trials, namely Contrave Obesity Research I (COR-I), COR-II, and COR-Behavior MODification (BMOD), enrolled patients with a BMI ≥ 27 kg/m^2 and at least one weight-related comorbid condi-

Table 2. Randomized, double-blind, placebo-controlled trials conducted for cardiovascular outcome trials of anti-obesity medications

Drug (trial)	Naltrexone/bupropion ER (LIGHT)[27]	Phentermine/topiramate ER (AQCLAIM)[32]	Semaglutide 2.4 mg (SELECT)[42]	Tirzepatide (SURMOUNT-MMO)[50]
Maintenance dose (maximum tolerated dose)	32/360 mg/day	15/92 mg/day	2.4 mg weekly	15 mg weekly
Population	n=8,910 Age ≥45 yr for men, ≥50 yr for women BMI 27–50 kg/m^2 WC ≥102 cm for men, ≥88 cm for women Preexisting CVD (32.1%) Type 2 diabetes mellitus with ≥2 risk factors (85.2%)	n=16,000 Age ≥45 yr BMI ≥27 kg/m^2 One of high stroke risk, high CVD risk or intermediate CVD risk	n=17,605 Age ≥45 yr BMI ≥27 kg/m^2 Established CVD with one or more of prior MI/stroke/PAD Without diabetes	n=15,000 Age ≥40 yr BMI ≥27 kg/m^2 Established CVD or the presence of CV risk factors Without diabetes
Primary outcome	Non-inferior 3-point MACE	Non-inferior MACE	Superior 3-point MACE	Time to first occurrence of any component event of composite
Results	Premature termination	Premature termination	In progress	In progress

ER, extended-release; LIGHT, Effect of Naltrexone-Bupropion on Major Adverse Cardiovascular Events in Overweight and Obese Patients With Cardiovascular Risk Factors; AQCLAIM, A Qysimia cardiovascular morbidity and mortality study in subjects with documented cardiovascular disease; SELECT, Semaglutide Effects on Heart Disease and Stroke in Patients With Overweight or Obesity; SURMOUNT-MMO, A Study of Tirzepatide (LY3298176) on the Reduction on Morbidity and Mortality in Adults With Obesity; BMI, body mass index; WC, waist circumference; CVD, cardiovascular disease; MI, myocardial infarction; PAD, peripheral arterial disease; CV, cardiovascular; MACE, major adverse cardiovascular events.

tion, such as hypertension.[23-25] The COR-Diabetes Mellitus (DM) trial specifically focused on patients with obesity and T2DM.[26] The NB group showed weight loss of 6.1% vs. 1.3%, 6.4% vs. 1.2%, 9.3% vs. 5.1%, and 5.0% vs. 1.8% compared to placebo in COR-I, COR-II, COR-BMOD, and COR-DM, respectively. In COR-DM, the NB group had significant glycosylated hemoglobin (HbA1c) reduction (0.6% vs. 0.1%).

Common AEs of NB include nausea, constipation, headache, vomiting, dizziness, insomnia, and dry mouth.[14] It is worth noting that NB can increase blood pressure and pulse despite greater weight loss. While the cardiovascular safety of NB was investigated in the LIGHT trial (Table 2), it was terminated prematurely after the study sponsor publicly released confidential favorable interim results after only 25% of expected vascular events had accrued, making it difficult to interpret the cardiovascular safety of this combination drug.[27]

NB components have been used for a long time, and NB itself has been a proven drug for almost 10 years. In terms of efficacy (Table 1),[11-19] AEs, and cost, NB shows intermediate characteristics among available AOMs.[20]

Phentermine/topiramate extended-release

The combination of P/T was FDA-approved for long-term weight management in 2012, making it the first combination agent for obesity treatment. P/T was later approved in Korea in 2019. However, it has limited approval in only a handful of countries and is not approved by the European Medicines Agency due to concerns regarding insufficient long-term data on its cardiovascular effects, as well as possible cognitive events and psychiatric effects.[28] Phentermine suppresses appetite by increasing epinephrine release in the hypothalamus, while topiramate's exact weight loss mechanism is not fully understood but involves dopamine release, glutamate receptor inhibition, and modulation of neuropeptide-Y, a hormone that stimulates food consumption.[29] The combination of P/T produces synergistic weight loss effects with a lower dosage than their independent usage.

The recommended dosing regimen starts with a daily dose of 3.75/23 mg for 2 weeks, followed by an increase to 7.5/46 mg. The minimum duration of treatment at this dose is 3 months before further increasing to the maximum dose of 15/92 mg through a 2-week bridging dose of 11.25/69 mg. If the patient experiences poor tolerability, a gradual titration down or discontinuation of the medication is advised to reduce the risk of seizures. The medication is taken orally once daily, unrelated to meals, and typically in the morning to prevent insomnia.

The 1-year CONQUER study evaluated the controlled-release phentermine plus topiramate combination in overweight and obese adults with 2+ comorbidities.[30] At 56 weeks, weight reductions were: placebo –1.4 kg, P/T 7.5/46 mg –8.1 kg, and P/T 15/92 mg –10.2 kg. Proportions achieving ≥5% and ≥10% weight loss respectively were: placebo 21% and 7%, P/T 7.5/46 mg 62%

and 37%, P/T 15/92 mg 70% and 48%. The SEQUEL study, a 2-year extension of the CONQUER trial, assessed sustained weight loss, showing changes from baseline of: placebo –1.8%, 7.5/46 mg –9.3%, 15/92 mg –10.5%.[31] The CONQUER trial revealed dose-related increases in anxiety, depression, and cognitive impairment.

P/T ranks high in terms of effectiveness among available obesity treatments (Table 1),[11-19] with moderate AEs and cost.[20] The cardiovascular benefits and safety have not yet been proven (Table 2).[32]

CURRENTLY AVAILABLE PEPTIDE AOMs

Since the 2010s, gastrointestinal peptide-based agents have emerged as a prominent therapeutic approach for obesity. Among these, glucagon-like peptide-1 receptor (GLP-1R) agonists are widely utilized in the treatment of obesity and diabetes. GLP-1 is secreted by L cells in the small intestine in response to food-related signals (Fig. 1).[33] It stimulates insulin secretion, inhibits glucagon secretion, and slows gastric emptying.[34] While neurons in the hypothalamus contribute to anorexigenic responses to peripheral GLP-1R agonism, they do not account for the complete spectrum of these responses.[23] The KMFDS has approved GLP-1 analogues, including liraglutide 3.0 mg and semaglutide 2.4 mg, for the treatment of obesity.

Liraglutide shares a 97% amino acid sequence similarity with human GLP-1(7-37), with the substitution of lysine to arginine at position 34, and it also has palmitic acid conjugated via a glutamate spacer at lysine in position 26.[35] On the other hand, semaglutide has an additional substitution of alanine to α-aminoisobutyric acid (Aib) at position 8, resulting in 94% similarity to human GLP-1(7-37), and it has a C18 fatty diacid chain conjugated via a spacer at lysine 26.[36]

The weight loss and diabetes improvement of liraglutide are mod-

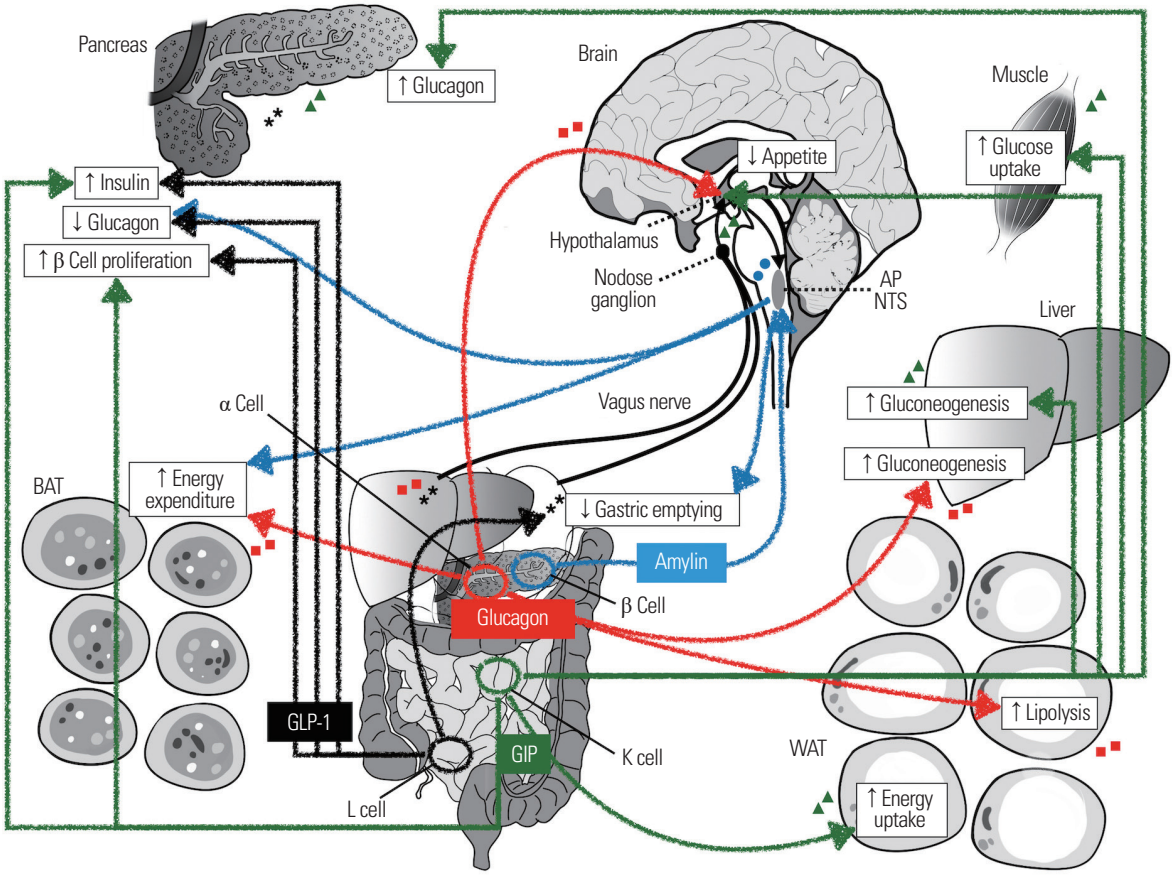

Figure 1. The direct physiologic effects of endogenous glucagon-like peptide-1 (GLP-1; black arrows), glucose-dependent insulinotropic polypeptide (GIP; green arrows), glucagon (red arrows), and amylin (blue arrows). The corresponding representation of these four peptides in target tissues is denoted by a black asterisk, green triangle, red rectangle, and blue circle, respectively. These four peptides exert their effects on the hypothalamus, either directly or indirectly through neuronal conduction, ultimately leading to a reduction in food intake. Adapted from Kim.[33] AP, area postrema; NTS, nucleaus tractus solitarius; BAT, brown adipose tissue; WAT, white adipose tissue.

erate, and the need for daily subcutaneous injections often discourages patients. There is a demand for a medication with stronger weight loss effects that can be administered less frequently or taken orally.

The amino acid substitutions in liraglutide and semaglutide decrease GLP-1's susceptibility to dipeptidyl peptidase-4 (DPP-4), and the fatty acid chain attached through a spacer enables binding with albumin, creating a long-acting GLP-1 analogue. The disparity in the attached fatty acids between semaglutide and liraglutide contributes to semaglutide's stronger effect, with semaglutide having a dicarboxylic acid form with two carboxyl groups, while liraglutide has a monocarboxylic acid form.[36]

The new GLP-1R agonist (GLP-1RA), semaglutide, has been developed in both a once-weekly injectable formulation and a once daily oral formulation, addressing the clinical limitations of liraglutide.

Liraglutide 3.0 mg

A lower dose of 1.8 mg liraglutide was initially approved in 2010 for T2DM. Liraglutide 3.0 mg became the first GLP-1RA approved for weight management in 2014 and in Korea in 2017. Recently, the KMFDS approved liraglutide for treating obesity in adolescents. The recommended starting dose is 0.6 mg daily via subcutaneous injection, gradually increased by 0.6 mg each week until reaching the target dose of 3.0 mg (Fig. 2).

Liraglutide's approval was based on three key trials: Satiety and Clinical Adiposity-Liraglutide (SCALE) Obesity and Prediabetes, SCALE Diabetes, and SCALE Maintenance.[37-39] In the SCALE Obesity and Prediabetes trial, which included obese participants with 61.2% having prediabetes, the liraglutide group achieved significantly higher weight loss compared to the placebo group (8.0% vs. 2.6%). Similar results were observed in the SCALE Diabetes trial, with the liraglutide group showing greater weight loss compared to placebo (6.0% vs. 2.0%). The SCALE Maintenance trial also

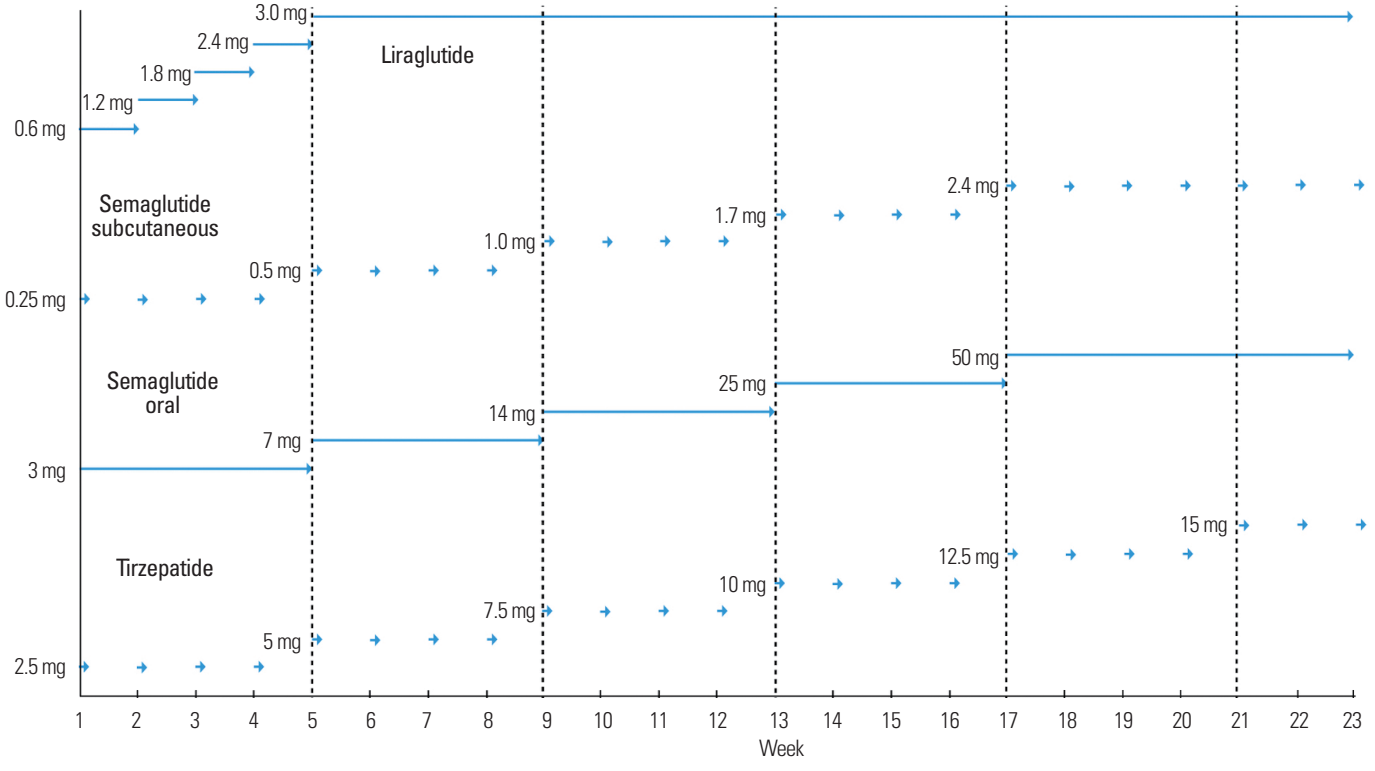

Figure 2. The recommended dosing schedule for liraglutide, semaglutide, and tirzepatide. Short arrows indicate a single dose, while long arrows represent daily administration. This dosing schedule reflects the recommended escalation and maintenance method outlined in the product manual. The recommended escalation method is to increase liraglutide by 0.6 mg every week until a maximum of 3.0 mg, increase semaglutide subcutaneous injection by 0.25–0.5–1.0–1.7–2.4 mg every 4 weeks, increase oral semaglutide by 3–7–14–25–50 mg every 4 weeks, and increase tirzepatide by 2.5 mg every 4 weeks until a maximum of 15 mg. However, it is important to individualize the escalation rate, maintenance dosage, and other factors based on the individual's response to treatment.

demonstrated additional weight loss in the liraglutide group (6.2% vs. 0.2%).

In the SCALE Obesity and Prediabetes trial, participants with prediabetes who completed the initial study were re-randomized to receive either liraglutide 3.0 mg or placebo for a 3-year assessment (2-year extension).[40] The trial revealed that the time to onset of diabetes was 2.7 times longer in the liraglutide group compared to the placebo group. Over the 3-year follow-up period, patients with prediabetes in the liraglutide group maintained a sustained weight loss of 6.1% compared to 1.9% in the placebo group. In the SCALE Sleep Apnea trial, liraglutide combined with health behavior modification significantly reduced apnea-hypopnea index events by –12.2 events per hour compared to –6.1 events per hour with behavior modification alone.[41]

The most common AEs in the liraglutide group included gastrointestinal symptoms (nausea, diarrhea, constipation, vomiting, and dyspepsia), as well as gallbladder-related events (cholelithiasis and cholecystitis), and an increase in resting heart rate.[37]

Liraglutide 3.0 mg, a proven drug with a nearly 10-year track record, has intermediate efficacy (Table 1)[11-19] and AEs. It is associated with more AEs than orlistat and comes with a higher cost.

Semaglutide 2.4 mg

Semaglutide injection 2.4 mg weekly is the newest GLP-1RA approved for chronic weight management in the United States in 2021 and in Korea in 2023. It was previously approved in 2017 as a subcutaneous injection once-weekly at a dose of 1.0 mg and in 2019 as an oral once daily dose of 14 mg for improving glycemic control in adults with T2DM. For the treatment of obesity, semaglutide is initiated at a dose of 0.25 mg once a week and increased every 4 weeks until reaching the full dose of 2.4 mg (Fig. 2). The solution is available in pre-filled disposable single dose pens in five different doses (0.25, 0.5, 1.0, 1.7, and 2.4 mg).

The efficacy of semaglutide 2.4 mg was assessed in the Semaglutide Treatment Effect in People with obesity (STEP) trials.[13-19] The STEP 1 trial demonstrated that the semaglutide group achieved a mean weight loss of –14.9% compared to –2.4% in the placebo group at week 68, with a higher percentage of participants in the semaglutide group achieving weight reductions of ≥ 5% (86.4% vs. 31.5%), ≥ 10% (69.1% vs. 12.0%), ≥ 15% (50.5% vs. 4.9%), and ≥ 20% (32.0% vs. 1.7%).[13] In the STEP 5 trial, the mean change in body weight from baseline to week 104 was –15.2% in the semaglutide group compared to –2.6% in the placebo group.[17] The most common AEs were gastrointestinal in nature, including nausea, constipation, diarrhea, vomiting, and abdominal pain, with most gastrointestinal AEs being mild to moderate and transient.[13] Headache, dizziness, and fatigue were more frequently reported in the semaglutide group.[13] Oral semaglutide 50 mg daily is currently under phase 3 clinical trials for the treatment of obesity.

Semaglutide is considered one of the most effective drugs among currently available AOMs (Table 1).[11-19] Research has shown that patients who discontinued semaglutide treatment and supportive lifestyle interventions regained approximately two-thirds of their lost weight within a year, indicating the potential need for long-term use. However, the high cost of semaglutide poses a significant financial burden for patients, both in the United States and Korea. As for the long-term health effects and AEs, conclusive evidence is still lacking (Table 2).[42]

WAITING APPROVAL FOR OBESITY TREATMENT

Tirzepatide

Glucose-dependent insulinotropic polypeptide (GIP) is an incretin hormone released by K cells of the small intestine in response to food intake. It has various effects, including appetite suppression in the central nervous system and stimulation of pancreatic beta cell growth, differentiation, and proliferation (Fig. 1).[33,43,44] However, GIP receptor (GIPR) agonism has not received much attention in the field of obesity and diabetes treatment. GIP exerts significant effects on adipocytes, such as increasing lipoprotein lipase, promoting lipogenesis, enhancing fatty acid and glucose uptake, and inhibiting lipolysis mediated by glucagon and adrenergic receptors.[44] Studies in mice with obesity and diabetes have shown that blocking GIP signaling can protect against or reverse metabolic disturbances associated with obesity.[44] In T2DM, GIPR expression in β cells is reduced, resulting in decreased responsiveness to GIP.[45] This down-regulation is caused by chronic hyperglycemia, and restoring normal blood glucose levels can restore GIP sensitivity.[45] Furthermore, GIP stimulates glucagon secretion even in people with T2DM

who have hyperglycemia.[46]

The role of GIPR agonism in the treatment of obesity and diabetes has become clearer with combination therapy involving GLP-1RA. By activating both GLP-1R and GIPR, blood glucose levels can be improved through GLP-1R activation, leading to enhanced GIPR response and further glucose improvement. GLP-1R stimulation can counteract the increased glucagon secretion caused by GIPR, and the activation of both appetite control receptors in the central nervous system can result in stronger appetite suppression.

Tirzepatide, approved by the FDA in 2022 for the treatment of T2DM, is a first-in-class dual agonist of the GIP/GLP-1Rs. It demonstrates a binding affinity to the GIPR comparable to that of native GIP itself, while displaying a lower binding affinity to the GLP-1R in comparison to native GLP-1.[47]

The starting dose of tirzepatide is 2.5 mg once-weekly, with a gradual increase of 2.5 mg every 4 weeks during the dose escalation period (Fig. 2). The maintenance dose can reach up to 15 mg once-weekly by week 20. The medication is available in pre-filled, disposable, single dose pens in five different doses: 2.5, 5, 7.5, 10, 12.5, and 15 mg.

Two research programs were conducted: the SURPASS trials for T2DM efficacy and the SURMOUNT trials for weight reduction. In the SURMOUNT-1 trial targeting non-diabetic patients with obesity, tirzepatide achieved an impressive 22.5% reduction in body weight after 72 weeks, surpassing other drugs.[48] This significant weight loss was accompanied by a favorable safety profile and improvements in secondary outcomes, including a delay in the onset of T2DM, reduced risk of decline in estimated glomerular filtration rate or renal death, and enhancements in quality of life measures. These positive outcomes contribute to the potential reduction of obesity-related morbidity and mortality.

The most common AEs with tirzepatide were gastrointestinal, including nausea, diarrhea, vomiting, constipation, and dyspepsia. These events were mostly mild to moderate in severity and primarily occurred during dose escalation.

Among the drugs that have undergone phase 3 trials, tirzepatide has shown to be the most effective, with generally mild to moderate AEs (Fig. 3).[8,13,23,31,37,40,48,49] Further experience is needed, similar to semaglutide, to determine the long-term benefits and safety of tirzepatide, especially regarding cardiovascular effects (Table 2).[50]

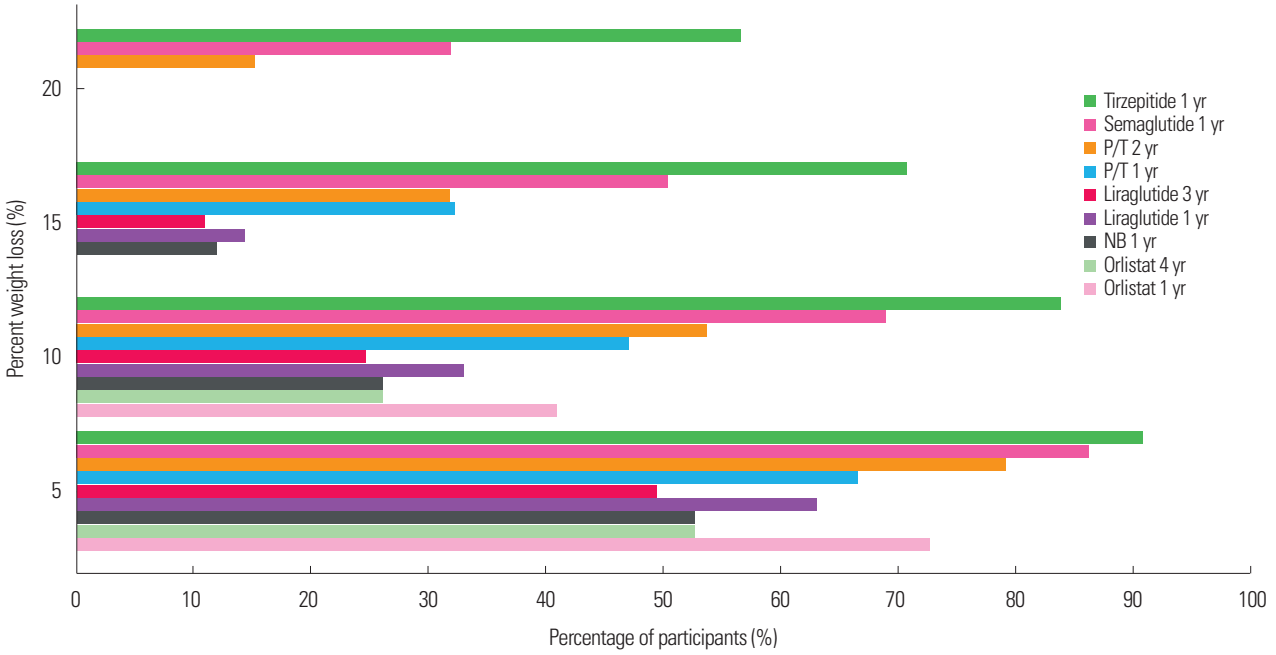

Figure 3. The percentage of participants achieving ≥5%, ≥10%, ≥15%, and ≥20% weight loss for each medication. Data were extracted from the following trials: XENical in the Prevention of Diabetes in Obese Subjects (XENDOS; orlistat),[8] Contrave Obesity Research I (COR-I; naltrexone/bupropion [NB] extended-release [ER]),[23] Satiety and Clinical Adiposity-Liraglutide (SCALE) Obesity and Prediabetes and its extension (liraglutide 3.0 mg),[37,40] EQUIP (phentermine/topiramate [P/T] ER 1 year),[49] SEQUEL (P/T ER 2 years),[31] Semaglutide Treatment Effect in People with obesity (STEP) 1 (semaglutide 2.4 mg),[13] and SURMOUNT-1 (tirzepatide 15 mg).[48]

PHASE 3 CLINICAL TRIAL DRUG

CagriSema

Obesity, a complex condition involving intricate mechanisms of weight regulation influenced by multiple hormones, can be effectively tackled by combining peptides that target different receptors. CagriSema, a fixed-dose combination of an amylin analogue and a GLP-1 analogue, addresses this need.

Amylin, a 37-amino acid peptide hormone, is released by pancreatic β cells after meals. It acts on the brainstem's area postrema, causing various physiological effects (Fig. 1).[51] These include inhibiting glucagon secretion, reducing food intake, delaying gastric emptying, and activating brown adipose tissue via the sympathetic nervous system, leading to increased energy expenditure.[51] Consequently, blood glucose levels decrease, promoting weight loss. Amylin receptor antagonism increases adipose tissue.[51] These effects are mediated through the autonomic nervous system's activation via the area postrema, rather than direct tissue action.

Pramlintide, an amylin receptor agonist, is used to treat type 1 diabetes mellitus and T2DM in the United States. By substituting three amino acids of human amylin with proline, it promotes weight loss in diabetes patients.[52] When combined with metreleptin, phentermine, and sibutramine, pramlintide showed superior weight loss outcomes.[53,54] However, its short duration of action requires multiple daily injections due to a 20-minute time to reach peak plasma concentration and an approximate 50-minute half-life.

To overcome pramlintide's short half-life and frequent administration, amylin receptor agonists like cagrilintide have been developed. Cagrilintide allows once-weekly subcutaneous administration by modifying the structure of human amylin, resulting in a longer half-life and pharmacological effects with weekly dosing. It involves substituting six amino acids and attaching a dicarboxylic acid form of fatty acid to the first amino acid lysine, similar to semaglutide.[55]

In a phase 1 clinical study, the concurrent administration of cagrilintide and semaglutide demonstrated significant weight loss outcomes.[56] The group receiving cagrilintide 2.4 mg+semaglutide 2.4 mg achieved a remarkable weight loss of 17.1% of initial body weight within just 20 weeks, including the dose escalation period, despite the study primarily focusing on evaluating pharmacokinetics and other parameters. The combination therapy shows promise for treating obesity. A phase 3 clinical study investigating CagriSema is currently underway.

DRUGS APPROACHING PHASE 3 CLINICAL TRIAL ENTRY

This section introduces three medications that are scheduled to enter phase 3 clinical trials, building upon their promising results from preclinical and early phase clinical studies. The forthcoming large-scale phase 3 trials will provide a clearer understanding of their effectiveness and safety through long-term administration.

LY3502970 (orforglipron)

The GLP-1R is a key target for obesity treatment. Most clinically used GLP-1 analogues are administered via subcutaneous injections, except for oral semaglutide, which has limitations. Oral semaglutide has low bioavailability, its absorption is affected by food and fluid intake, and it requires specific administration instructions. This complex dosing regimen can impact medication adherence. A non-peptide GLP-1R ligand, like LY3502970, shows promise as an easy-to-administer, consistently absorbed, and clinically effective option. LY3502970 has demonstrated favorable results in preclinical and early phase clinical trials, prompting a phase 3 study for obesity and T2DM.

LY3502970 interacts with GLP-1R in a slightly different manner compared to native GLP-1. Native GLP-1 binds to transmembrane (TM) domains 1–3 and 5–7 of GLP-1R, while LY3502970 binds to the extracellular domain (ECD) as well as TM 1, 2, 3, 7, and extracellular loop 2 of GLP-1R. *In vitro* experiments have shown that LY3502970 acts as a biased ligand for GLP-1R, increasing cyclic adenosine monophosphate concentration without significantly elevating β-arrestin levels (Fig. 4).[57-60] This suggests a favorable mechanism of action from a pharmacological standpoint.[57]

GLP-1R belongs to the class B of G-protein coupled receptors (GPCRs), and LY3502970 does not exhibit activity against other class B GPCRs. Interestingly, LY3502970 does not demonstrate activity against GLP-1R in mice and other species, possibly due to species-specific differences in the amino acid sequence of the ECD of GLP-1R.[58]

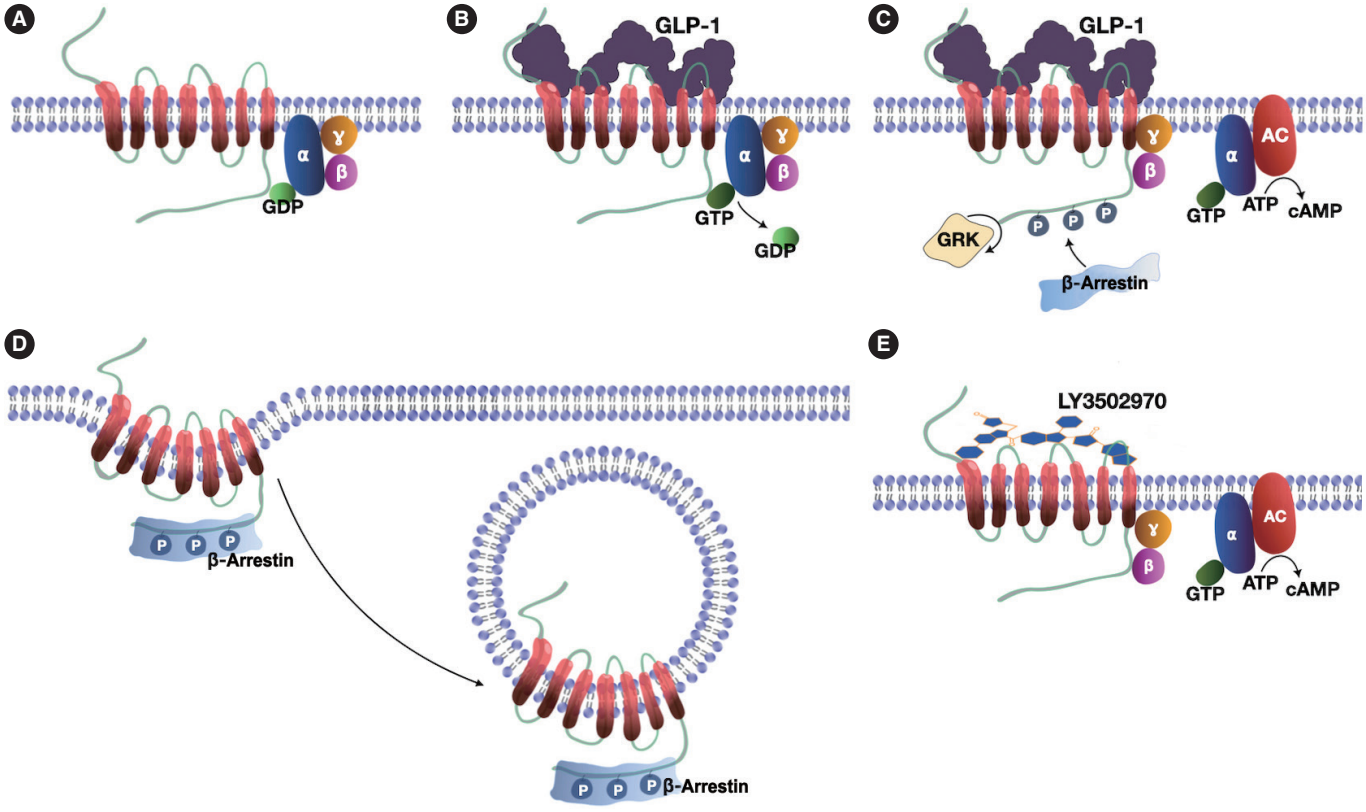

Figure 4. The manner of action on the glucagon-like peptide-1 (GLP-1) receptor differs between native GLP-1 and LY3502970 (orforglipron). The GLP-1 receptor belongs to the class B G-protein coupled receptor (GPCR) family. Schematic explanations A to D illustrate the classic model of G-protein-mediated activation and β-arrestin-related desensitization in GLP-1 receptor agonism by native GLP-1, while E demonstrates the biased agonism of LY3502970 on the GLP-1 receptor. (A) Inactive state of the GLP-1 receptor. (B) Activated GLP-1 receptor with attached GLP-1, leading to the substitution of guanosine diphosphate (GDP) with guanosine triphosphate (GTP) on the α subunit of the Gs protein (Gαs). (C) Gα dissociates from the G-protein and stimulates adenyl cyclase (AC), converting adenosine triphosphate (ATP) to cyclic adenosine monophosphate (cAMP) and resulting in elevated cAMP levels. Simultaneously, the C-terminal tail of the GLP-1 receptor is phosphorylated by G protein-coupled receptor kinase (GRK), allowing β-arrestin to bind to the GLP-1 receptor, forming a complex. (D) Internalization of the GLP-1 receptor by β-arrestin. (E) The biased agonism of LY3502970 primarily proceeds through the cAMP pathway with reduced β-arrestin recruitment.[58] This biased agonism is also exhibited by TT-OAD2, another orally administered non-peptidic GLP-1R agonist compound.[59] However, it is important to note that GPCR signaling is significantly more complex. GPCRs can couple with various G-protein families, activate them differentially depending on conditions, and also engage non-G-protein-related signaling pathways.[60]

Early phase studies using LY3502970 have reported excellent efficacy and safety; however, detailed reports on these results have not been published. According to the presentation of phase 1 study results, the most commonly reported side effects were vomiting, nausea, constipation, and headache. The pharmacokinetics showed dose-proportional behavior, with a mean half-life ranging from 48.1 to 67.5 hours across the dose range when administered daily for 28 days. Gastric emptying was delayed, and there were significant decreases in fasting glucose and body weight.[61] There is no available record on how LY3502970 acts on appetite centers in the brain.

BI 456906

Until now, most AOMs have primarily focused on appetite suppression as the main mechanism of action. However, it is more reasonable to adopt a strategy that promotes both appetite suppression and energy expenditure for effective weight loss or weight maintenance. While substances that increase energy expenditure exist, their safety for clinical use has not been established.

Glucagon, known for increasing energy expenditure,[62] has been underutilized beyond hypoglycemia treatment due to its impact on blood glucose levels. However, it also has metabolic functions, including regulating food intake, promoting satiety, lipid homeostasis, insulin secretion, and energy expenditure. The concept of simultaneous stimulation of GLP-1R and GLP-1R glucagon receptor (GCGR), as seen with oxyntomodulin, an endogenous weak agonist for both GLP-1R and GCGR, offers a weight loss strategy. By

activating both receptors, glucagon's undesired effects can be mitigated while addressing obesity and metabolic complications. The synergy of appetite suppression and increased energy expenditure is effective for weight loss. Unfortunately, oxyntomodulin's weak potency and short half-life limit its clinical suitability.

Peptide engineering, exemplified by tirzepatide, allows the development of multi-receptor agonists. BI 456906 is a dual agonist for GLP-1R and GCGR, designed for obesity and nonalcoholic steatohepatitis (NASH) treatment. However, it exhibits biased activity towards GLP-1R, with full activation of GLP-1R and partial activation of GCGR at therapeutic exposure. It is a potent, acylated peptide incorporating a C18 fatty acid to extend its half-life, supporting once-weekly dosing in humans. BI 456906, structurally modified from glucagon, resists proteolysis by DPP-4 due to C-terminal amidation.

Phase 1 studies of BI 456906 revealed that the median time to reach maximum concentration in European and Japanese studies ranged from 12 to 24 hours and 6 to 28 hours, respectively.[63,64] Common AEs of BI 456906 included nausea, eructation, dyspepsia, vomiting, diarrhea, abdominal pain, and headache.[63] In the Japanese clinical trial, there were two instances of severe vomiting and diarrhea, as well as two cases of treatment discontinuation due to AEs, including one case of mild amylase increase and one case of vomiting requiring hospitalization.[64] A significant number of participants experienced an increase in heart rate of more than 10 bpm.[64] Maximum placebo-corrected weight loss after 16 weeks was –13.8%, and BI 456906 exhibited a dose-independent half-life exceeding 100 hours.[63]

Clinical studies suggest that GLP-1 analogues, including semaglutide, face challenges in improving liver fibrosis or resolving NASH, as GLP-1R has not been found in hepatocytes.[65,66] In contrast, drugs targeting GCGR, which directly affects hepatocyte function, have a high potential to positively impact NASH.

LY3437943 (retartrutide)

Given the benefits of dual agonists targeting GIPR/GLP-1R and GLP-1R/GCGR, it is hypothesized that a triple agonist simultaneously targeting all three receptors has the potential to provide an even more effective therapeutic approach for achieving improved glycemic control and weight loss compared to single or dual receptor agonists. LY3437943, a 39-amino acid peptide derived from a GIP peptide backbone, exhibits triple agonist activity at GCGR, GIPR, and GLP-1R. It incorporates Aib for stability against DPP-4 cleavage. The peptide backbone is linked to a C20 fatty diacid moiety at the 17th lysine residue, facilitating albumin binding to prolong its pharmacokinetic half-life while maintaining desired pharmacological properties. LY3437943 is 2.9-fold less potent than human glucagon at the human GCGR, 8.9-fold more potent than GIP at the human GIPR, and 2.5-fold less potent than GLP-1 at the human GLP-1R. It exhibits balanced activity at GCGR and GLP-1R but higher activity at GIPR.[67]

Phase 1 studies of LY3437943 have shown an average half-life of approximately 6 days.[67,68] In a phase 1b multiple-ascending dose trial with individuals with T2DM, gastrointestinal disorders like diarrhea, nausea, and vomiting were common treatment-emergent AEs. Due to the coronavirus disease 2019 pandemic, study completion was limited, with no participants completing the study in the 0.5 mg group and only one in the 1.5 mg group. However, meaningful results were obtained from the 3, 3/6, and 3/6/9/12 mg groups.[68] Despite the stimulation of GCGR by this triple agonist, the higher dosage groups showed significant reductions in fasting and postprandial plasma glucose levels and HbA1c.[68] The stronger activity at GIPR compared to GCGR and GLP-1R may explain the positive effects. Body weight decreased in a dose-dependent manner, with an approximately 9 kg (10%) reduction observed at the highest dosage.[68] These results are particularly promising given the short treatment duration and the participants' low body weight. LY3437943 treatment was associated with decreases in blood pressure and an increase in heart rate.[68] Additionally, LY3437943 led to a decrease in serum aminotransferase concentrations.[68]

CONCLUSION

Due to the global obesity epidemic, the demand for effective and safe AOMs is high. In Korea, pharmacotherapy is strongly recommended by KSSO for Korean adults with a BMI of 25 kg/m^2 or higher who have not achieved weight loss through non-pharmacological treatments. Currently, five AOMs are approved for long-term weight management: orlistat, NB ER, P/T ER, liraglutide, and semaglutide. Tirzepatide awaits approval, and CagriSema and oral sema-

glutide are currently in phase 3 trials. Other drugs such as orforglipron, BI 456906, and retartrutide are advancing to phase 3 studies.

While the new generation of AOMs shows improved efficacy, there are individuals who respond poorly or do not respond at all to each drug. This underscores the importance of personalized obesity therapy. There is also concern about the misuse of AOMs solely for aesthetic purposes by individuals who do not meet the appropriate indications. Moreover, financial barriers and health inequalities are additional concerns. Physicians play a critical role in identifying individuals who genuinely require treatment and selecting the appropriate AOMs to ensure maximum health benefits.

CONFLICTS OF INTEREST

Kyoung-Kon Kim has participated in several clinical trials of medications mentioned in this manuscript. However, the content of this manuscript has not been directly or indirectly influenced by any pharmaceutical company.

ACKNOWLEDGMENTS

The authors would like to express gratitude to Johng Ho Kim for his assistance in the production of figures.

AUTHOR CONTRIBUTIONS

Study concept and design: EJ and KKK; acquisition of data: EJ and KKK; analysis and interpretation of data: all authors; drafting of the manuscript: EJ and KKK; critical revision of the manuscript: all authors; administrative, technical, or material support: KYL and KKK; and study supervision: KKK.

REFERENCES

1. Ryan DH, Yockey SR. Weight loss and improvement in comorbidity: differences at 5%, 10%, 15%, and over. Curr Obes Rep 2017;6:187-94.
2. Arterburn DE, Telem DA, Kushner RF, Courcoulas AP. Benefits and risks of bariatric surgery in adults: a review. JAMA 2020;324:879-87.
3. Velapati SR, Shah M, Kuchkuntla AR, Abu-Dayyeh B, Grothe K, Hurt RT, et al. Weight regain after bariatric surgery: prevalence, etiology, and treatment. Curr Nutr Rep 2018;7:329-34.
4. Kim KK, Haam JH, Kim BT, Kim EM, Park JH, Rhee SY, et al. Evaluation and treatment of obesity and its comorbidities: 2022 update of clinical practice guidelines for obesity by the Korean Society for the Study of Obesity. J Obes Metab Syndr 2023;32:1-24.
5. Jensen MD, Ryan DH, Apovian CM, Ard JD, Comuzzie AG, Donato KA, et al. 2013 AHA/ACC/TOS guideline for the management of overweight and obesity in adults: a report of the American College of Cardiology/American Heart Association task force on practice guidelines and the obesity society. Circulation 2014;129(25 Suppl 2):S102-38.
6. Apovian CM, Aronne LJ, Bessesen DH, McDonnell ME, Murad MH, Pagotto U, et al. Pharmacological management of obesity: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2015;100:342-62.
7. Guerciolini R. Mode of action of orlistat. Int J Obes Relat Metab Disord 1997;21 Suppl 3:S12-23.
8. 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;27:155-61.
9. Padwal R, Li SK, Lau DC. Long-term pharmacotherapy for obesity and overweight. Cochrane Database Syst Rev 2004; 2003:CD004094.
10. Ardissino M, Vincent M, Hines O, Amin R, Eichhorn C, Tang AR, et al. Long-term cardiovascular outcomes after orlistat therapy in patients with obesity: a nationwide, propensity-score matched cohort study. Eur Heart J Cardiovasc Pharmacother 2022;8:179-86.
11. Khera R, Murad MH, Chandar AK, Dulai PS, Wang Z, Prokop LJ, et al. Association of pharmacological treatments for obesity with weight loss and adverse events: a systematic review and meta-analysis. JAMA 2016;315:2424-34.
12. Khera R, Pandey A, Chandar AK, Murad MH, Prokop LJ, Neeland IJ, et al. Effects of weight-loss medications on cardiometabolic risk profiles: a systematic review and network

meta-analysis. Gastroenterology 2018;154:1309-19.
13. 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;384:989-1002.
14. 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, double-dummy, placebo-controlled, phase 3 trial. Lancet 2021;397:971-84.
15. 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;325:1403-13.
16. Rubino D, Abrahamsson N, Davies M, Hesse D, Greenway FL, Jensen C, et al. Effect of continued weekly subcutaneous semaglutide vs placebo on weight loss maintenance in adults with overweight or obesity: the STEP 4 randomized clinical trial. JAMA 2021;325:1414-25.
17. Garvey WT, Batterham RL, Bhatta M, Buscemi S, Christensen LN, Frias JP, et al. Two-year effects of semaglutide in adults with overweight or obesity: the STEP 5 trial. Nat Med 2022; 28:2083-91.
18. Kadowaki T, Isendahl J, Khalid U, Lee SY, Nishida T, Ogawa W, et al. Semaglutide once a week in adults with overweight or obesity, with or without type 2 diabetes in an east Asian population (STEP 6): a randomised, double-blind, double-dummy, placebo-controlled, phase 3a trial. Lancet Diabetes Endocrinol 2022;10:193-206.
19. 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;327:138-50.
20. Bessesen DH, Van Gaal LF. Progress and challenges in anti-obesity pharmacotherapy. Lancet Diabetes Endocrinol 2018; 6:237-48.
21. Anderson JW, Greenway FL, Fujioka K, Gadde KM, McKenney J, O'Neil PM. Bupropion SR enhances weight loss: a 48-week double-blind, placebo- controlled trial. Obes Res 2002; 10:633-41.
22. Billes SK, Sinnayah P, Cowley MA. Naltrexone/bupropion for obesity: an investigational combination pharmacotherapy for weight loss. Pharmacol Res 2014;84:1-11.
23. 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, placebo-controlled, phase 3 trial. Lancet 2010;376:595-605.
24. 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;21:935-43.
25. Wadden TA, Foreyt JP, Foster GD, Hill JO, Klein S, O'Neil PM, et al. Weight loss with naltrexone SR/bupropion SR combination therapy as an adjunct to behavior modification: the COR-BMOD trial. Obesity (Silver Spring) 2011;19:110-20.
26. 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;36:4022-9.
27. Nissen SE, Wolski KE, Prcela L, Wadden T, Buse JB, Bakris G, et al. Effect of naltrexone-bupropion on major adverse cardiovascular events in overweight and obese patients with cardiovascular risk factors: a randomized clinical trial. JAMA 2016; 315:990-1004.
28. Alobaida M, Alrumayh A, Oguntade AS, Al-Amodi F, Bwalya M. Cardiovascular safety and superiority of anti-obesity medications. Diabetes Metab Syndr Obes 2021;14:3199-208.
29. Cosentino G, Conrad AO, Uwaifo GI. Phentermine and topiramate for the management of obesity: a review. Drug Des Devel Ther 2011;7:267-78.
30. 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, placebo-controlled, phase 3 trial. Lancet 2011; 377:1341-52.
31. Garvey WT, Ryan DH, Look M, Gadde KM, Allison DB, Pe-

terson CA, et al. Two-year sustained weight loss and metabolic benefits with controlled-release phentermine/topiramate in obese and overweight adults (SEQUEL): a randomized, placebo-controlled, phase 3 extension study. Am J Clin Nutr 2012;95:297-308.
32. European Union Clinical Trials Register. Clinical trials for AQCLAIM [Internet]. European Medicines Agency; 2023 [cited 2023 Jun 22]. Available from: https://www.clinicaltrialsregister.eu/ctr-search/search?query=AQCLAIM
33. Kim KK. Peptides in obesity treatment. Arch Obes Metab 2022;1:4-13.
34. Drucker DJ. Mechanisms of action and therapeutic application of glucagon-like peptide-1. Cell Metab 2018;27:740-56.
35. Knudsen LB. Liraglutide: the therapeutic promise from animal models. Int J Clin Pract Suppl 2010;167:4-11.
36. Knudsen LB, Lau J. The discovery and development of liraglutide and semaglutide. Front Endocrinol (Lausanne) 2019;10:155.
37. 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;373:11-22.
38. Davies MJ, Bergenstal R, Bode B, Kushner RF, Lewin A, Skjøth TV, et al. Efficacy of liraglutide for weight loss among patients with type 2 diabetes: the SCALE diabetes randomized clinical trial. JAMA 2015;314:687-99.
39. Wadden TA, Hollander P, Klein S, Niswender K, Woo V, Hale PM, et al. Weight maintenance and additional weight loss with liraglutide after low-calorie-diet-induced weight loss: the SCALE maintenance randomized study. Int J Obes (Lond) 2013;37:1443-51.
40. 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;389:1399-409.
41. Blackman A, Foster GD, Zammit G, Rosenberg R, Aronne L, Wadden T, et al. Effect of liraglutide 3.0 mg in individuals with obesity and moderate or severe obstructive sleep apnea: the SCALE Sleep Apnea randomized clinical trial. Int J Obes (Lond) 2016;40:1310-9.
42. Lingvay I, Brown-Frandsen K, Colhoun HM, Deanfield J, Emerson SS, Esbjerg S, et al. Semaglutide for cardiovascular event reduction in people with overweight or obesity: SELECT study baseline characteristics. Obesity (Silver Spring) 2023;31:111-22.
43. Zhang Q, Delessa CT, Augustin R, Bakhti M, Colldén G, Drucker DJ, et al. The glucose-dependent insulinotropic polypeptide (GIP) regulates body weight and food intake via CNS-GIPR signaling. Cell Metab 2021;33:833-44.
44. Irwin N, Flatt PR. Therapeutic potential for GIP receptor agonists and antagonists. Best Pract Res Clin Endocrinol Metab 2009;23:499-512.
45. Piteau S, Olver A, Kim SJ, Winter K, Pospisilik JA, Lynn F, et al. Reversal of islet GIP receptor down-regulation and resistance to GIP by reducing hyperglycemia in the Zucker rat. Biochem Biophys Res Commun 2007;362:1007-12.
46. El K, Campbell JE. The role of GIP in α-cells and glucagon secretion. Peptides 2020;125:170213.
47. Coskun T, Sloop KW, Loghin C, Alsina-Fernandez J, Urva S, Bokvist KB, et al. LY3298176, a novel dual GIP and GLP-1 receptor agonist for the treatment of type 2 diabetes mellitus: from discovery to clinical proof of concept. Mol Metab 2018;18:3-14.
48. 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;387:205-16.
49. Allison DB, Gadde KM, Garvey WT, Peterson CA, Schwiers ML, Najarian T, et al. Controlled-release phentermine/topiramate in severely obese adults: a randomized controlled trial (EQUIP). Obesity (Silver Spring) 2012;20:330-42.
50. Clinicaltrials.gov. A Study of Tirzepatide (LY3298176) on the Reduction on Morbidity and Mortality in Adults With Obesity (SURMOUNT-MMO) [Internet]. clinicaltrials.gov; 2023 [cited 2023 Jun 22]. Available from: https://classic.clinicaltrials.gov/ct2/show/NCT05556512
51. Hay DL, Chen S, Lutz TA, Parkes DG, Roth JD. Amylin: pharmacology, physiology, and clinical potential. Pharmacol Rev 2015;67:564-600.
52. Dunican KC, Adams NM, Desilets AR. The role of pramlint-

ide for weight loss. Ann Pharmacother 2010;44:538-45.
53. Ravussin E, Smith SR, Mitchell JA, Shringarpure R, Shan K, Maier H, et al. Enhanced weight loss with pramlintide/metreleptin: an integrated neurohormonal approach to obesity pharmacotherapy. Obesity (Silver Spring) 2009;17:1736-43.
54. Aronne LJ, Halseth AE, Burns CM, Miller S, Shen LZ. Enhanced weight loss following coadministration of pramlintide with sibutramine or phentermine in a multicenter trial. Obesity (Silver Spring) 2010;18:1739-46.
55. Kruse T, Hansen JL, Dahl K, Schäffer L, Sensfuss U, Poulsen C, et al. Development of cagrilintide, a long-acting amylin analogue. J Med Chem 2021;64:11183-94.
56. Enebo LB, Berthelsen KK, Kankam M, Lund MT, Rubino DM, Satylganova A, et al. Safety, tolerability, pharmacokinetics, and pharmacodynamics of concomitant administration of multiple doses of cagrilintide with semaglutide 2·4 mg for weight management: a randomised, controlled, phase 1b trial. Lancet 2021;397:1736-48.
57. Kawai T, Sun B, Yoshino H, Feng D, Suzuki Y, Fukazawa M, et al. Structural basis for GLP-1 receptor activation by LY3502970, an orally active nonpeptide agonist. Proc Natl Acad Sci U S A 2020;117:29959-67.
58. Graaf Cd, Donnelly D, Wootten D, Lau J, Sexton PM, Miller LJ, et al. Glucagon-like peptide-1 and its class B G protein-coupled receptors: a long march to therapeutic successes. Pharmacol Rev 2016;68:954-1013.
59. Zhao P, Liang YL, Belousoff MJ, Deganutti G, Fletcher MM, Willard FS, et al. Activation of the GLP-1 receptor by a non-peptidic agonist. Nature 2020;577:432-6.
60. Luttrell LM, Maudsley S, Bohn LM. Fulfilling the promise of "biased" G protein-coupled receptor agonism. Mol Pharmacol 2015;88:579-88.
61. Pratt EJ, Ma X, Liu R, Robins DA, Sloop K, Benson C. 336-OR: A first-in-human single-and multiple-ascending dose study evaluating safety, tolerability, pharmacokinetics, and pharmacodynamics of a novel oral nonpeptide Glp-1 receptor agonist in healthy subjects. Diabetes 2022;71(Supplement 1):336-OR.
62. Kleinert M, Sachs S, Habegger KM, Hofmann SM, Müller TD. Glucagon regulation of energy expenditure. Int J Mol Sci 2019;20:5407.
63. Jungnik A, Arrubla Martinez J, Plum-Mörschel L, Kapitza C, Lamers D, Thamer C, et al. Phase I studies of the safety, tolerability, pharmacokinetics and pharmacodynamics of the dual glucagon receptor/glucagon-like peptide-1 receptor agonist BI 456906. Diabetes Obes Metab 2023;25:1011-23.
64. Yazawa R, Ishida M, Balavarca Y, Hennige AM. A randomized phase I study of the safety, tolerability, pharmacokinetics and pharmacodynamics of BI 456906, a dual glucagon receptor/glucagon-like peptide-1 receptor agonist, in healthy Japanese men with overweight/obesity. Diabetes Obes Metab 2023;25:1973-84.
65. Newsome PN, Buchholtz K, Cusi K, Linder M, Okanoue T, Ratziu V, et al. A placebo-controlled trial of subcutaneous semaglutide in nonalcoholic steatohepatitis. N Engl J Med 2021;384:1113-24.
66. Loomba R, Abdelmalek MF, Armstrong MJ, Jara M, Kjær MS, Krarup N, et al. Semaglutide 2·4 mg once weekly in patients with non-alcoholic steatohepatitis-related cirrhosis: a randomised, placebo-controlled phase 2 trial. Lancet Gastroenterol Hepatol 2023;8:511-22.
67. Coskun T, Urva S, Roell WC, Qu H, Loghin C, Moyers JS, et al. LY3437943, a novel triple glucagon, GIP, and GLP-1 receptor agonist for glycemic control and weight loss: from discovery to clinical proof of concept. Cell Metab 2022;34:1234-47.
68. Urva S, Coskun T, Loh MT, Du Y, Thomas MK, Gurbuz S, et al. LY3437943, a novel triple GIP, GLP-1, and glucagon receptor agonist in people with type 2 diabetes: a phase 1b, multicentre, double-blind, placebo-controlled, randomised, multiple-ascending dose trial. Lancet 2022;400:1869-81.