



# Long-Term Efficacy and Safety of Anti-Obesity Treatment: Where Do We Stand?

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Accepted: 17 December 2020 / Published online: 6 January 2021

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## Abstract

**Purpose of Review** As a chronic and relapsing disease, obesity impairs metabolism and causes cardiovascular diseases. Although behavioral modification is important for the treatment of obesity, it is difficult to achieve an ideal weight or sustain the process of long-term weight loss. Therefore, the obesity control guidelines strongly recommend lifestyle interventions along with medical treatment for patients who are overweight. There is sufficient evidence supporting that pharmacotherapy in combination with behavior-based interventions can result in significant weight loss and improved cardiometabolism.

**Recent Findings** Recent meta-analyses of new anti-obesity drugs and their weight-loss efficacy have shown that the overall placebo-subtracted weight reduction (%) for at least 12 months ranged from 2.9 to 6.8% for the following drugs: phentermine/topiramate (6.8%), liraglutide (5.4%), naltrexone/bupropion (4.0%), orlistat (2.9%), and lorcaserin (3.1%). However, very recently, on February 13, 2020, the US Food and Drug Administration (FDA) ordered the withdrawal of lorcaserin from markets, as a clinical trial to assess drug safety showed an increased risk of cancer. Currently, the anti-obesity medications that have been approved by the FDA for chronic weight management are orlistat, phentermine/topiramate, naltrexone/bupropion, and liraglutide. However, they are costly and may have adverse effects in some individuals. Therefore, drug therapy should be initiated in obese individuals after weighing its benefits and risks.

**Summary** One of the strategies for long-term obesity control is that anti-obesity medications should be tailored for specific patients depending on their chronic conditions, comorbidities, and preferences.

**Keywords** Anti-obesity drugs · Orlistat · Phentermine/topiramate · Naltrexone/bupropion · Liraglutide · Weight loss medications

## Introduction

Ischemic heart disease, cancer, and stroke are the leading causes of death worldwide, in recent years [1]. These diseases

are related to the “epidemic of obesity,” one of the major global health concerns [2]. Due to high-calorie diet and sedentary lifestyle, obesity is highly prevalent [3]. In particular, lockdown measures to limit the transmission of coronavirus have negatively affected a range of weight management practices, including physical activity and healthy eating. Thus, the obesity epidemic is estimated to worsen [4]. In addition to being a major risk factor for cardiovascular disease (CVD) and all-cause mortality [5], high body mass index (BMI) is now also considered a risk factor for the coronavirus disease 2019 (COVID-19) mortality [6]. Therefore, efforts to control weight and minimize regain during the COVID-19 crisis should be emphasized in patients with obesity.

The fundamental approach for weight reduction is to induce a negative energy balance by increasing physical activities and starting a calorie restriction diet [7]. Guidelines on obesity control define clinically significant weight loss as at least a 5% reduction in weight from the baseline level and associated with improvements in cardio-metabolic risk factors [8]. However, as the rate of long-term adherence to lifestyle

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This article is part of the Topical Collection on *Metabolism*

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modifications is low, most patients with obesity lose only modest weight with non-pharmacological interventions alone [7]. Even if they achieve significant weight reduction, approximately one-third, more than half, and almost the total population with obesity return to their original weight within a year, 2 years, and 5 years, respectively [9]. Thus, currently, most guidelines on obesity control strongly recommend medical treatment for patients with obesity who cannot achieve adequate weight loss from lifestyle interventions [8, 9]. Energy intake in the form of food is highly controlled by the central and peripheral hormonal signaling, with different mechanisms targeting various factors in diverse pathways [10]. Numerous medications for obesity treatment have been developed mainly by exploiting the following mechanisms: (1) reducing appetite and thereby energy intake, (2) promoting energy expenditure, and (3) lowering calorie absorption [7–9]. Some drugs in the development stage were expected to be effective in the treatment of obesity *in vivo* and theoretically, but they were abandoned due to minimal weight loss effect in additional animal studies and early clinical trials [11]. During the last few decades, some anti-obesity drugs were used to treat morbid obesity; however, many of them were removed from the market owing to long-term side effects, particularly cardiovascular issues [12]. Since then, anti-obesity drug development process focusses on both weight loss efficacy and cardiovascular safety. In recent years, the US Food and Drug Administration (FDA) has approved newer pharmacological options that were developed more cautiously and elucidated safety as well as efficacy [13]. As these anti-obesity drugs are approved for long-term management, they provide a better appreciation of the complex, chronic, and relapsing nature of obesity [14]. Most importantly, the availability of different types of medications offers healthcare providers with more options to suggest tailored treatment plans for their patients. In this review, we aimed to provide an overview of the efficacy and safety of anti-obesity drugs that manages long-term obesity.

### What We Learned from the Withdrawn Anti-Obesity Drugs

Many promising weight-loss drugs have been withdrawn from the market due to their life-threatening side effects. A few such drugs and the adverse effects known to be associated with them are aminorex (pulmonary hypertension), fenfluramine (cardiac valvulopathy), dexfenfluramine (valvulopathy), phenylpropanolamine (stroke), rimonabant (suicidal ideation and behavior), sibutramine (myocardial infarction and stroke), and the most recent drug, lorcaserin (cancer) [12, 15]. After the withdrawal of sibutramine in 2010, the FDA sought cardiovascular-safety data for new anti-obesity drugs [16].

### Lorcaserin

Since its FDA approval in 2012, lorcaserin (Belviq®) was one of the most frequently prescribed weight-loss drugs until early 2020. However, lorcaserin did not gain an approval from the European Medical Agency (EMA), as its preclinical data revealed the potential risk of breast cancer, psychiatric adverse effects, including aggravation of depression, suicidal ideation, and psychosis, and valvulopathy. There are more than 14 serotonin receptor subtypes that regulate different physiological functions (ranging from hallucinations to muscle contraction) [17]. Some serotonin agonists exert anorectic effects (increase satiety that results in reduced food intake) by stimulating the proopiomelanocortin (POMC) receptors in the arcuate nucleus of the hypothalamus [18]. The side effects of non-specific serotonin agonists, such as fenfluramine and dexfenfluramine, are caused due to the stimulation of the peripheral 5-hydroxytryptamine 2B (5-HT<sub>2b</sub>) receptors. One of the predominant agonists of the 5-HT<sub>2b</sub> receptor is fenfluramine that is believed to cause adverse CVD effects by stimulating mitotic activity, resulting in cell overgrowth within the valve leaflets [19]. Owing to its high selectivity (15-fold and 100-fold more than that for 5-HT<sub>2a</sub> and 5-HT<sub>2b</sub> receptors, respectively) for the 5-HT<sub>2c</sub> receptor, lorcaserin can suppress appetite and hunger without triggering pulmonary hypertension or valvular heart defects [20]. In addition, many studies have suggested that lorcaserin has multiple psychological effects, such as reduced craving, impulsivity, and elevated satiety, which contribute to weight loss.

During the initial submission in 2009, lorcaserin failed to obtain FDA approval, as the non-clinical carcinogenicity studies revealed an increased incidence of several types of tumors in rats assigned to the lorcaserin-treated group [21]. However, in the clinical trials conducted later, the efficacy of lorcaserin met the regulatory standard (47% of participants treated with lorcaserin achieved at least 5% weight loss after 1 year as compared with 23% of those treated with placebo). No cancer-related safety issues arose during the 1-year trial involving more than 2400 lorcaserin-treated patients [16]. On January 14, 2020, however, the FDA issued a potential signal indicating an increased risk of cancer and cancer-related mortality associated with the use of lorcaserin [22]. Soon after, on February 13, 2020, the FDA officially issued a warning to the drug manufacturer to voluntarily withdraw lorcaserin from the market, as the potential risks of the drug outweighed its benefits [23]. This was announced after the FDA reviewed the Cardiovascular and Metabolic Effects of Lorcaserin in Overweight and Obese Patients – Thrombolysis in Myocardial Infarction 61 (CAMELLIA-TIMI 61) clinical trial data to evaluate the risk of CVD [24]. This randomized, double-blind, placebo-controlled, multicenter, and parallel group trial, involving 12,000 women and men who were overweight, was conducted between January 2014 and June 2018 in the

USA, Europe, Australia, Canada, Mexico, the Bahamas, New Zealand, and South America. All the patients had a history of CVD, whereas the male and female patients of at least 50 and 55 years of age, respectively, had type 2 diabetes mellitus (T2DM) and at least one additional CVD risk factor. They were assigned randomly to either a lorcaserin 10 mg BID or a placebo group. Approximately 96% of patients completed the trial, of which 62% remained on treatment till the end of the study. The median follow-up time was 3 years and 3 months. The primary safety analysis showed no major difference between the lorcaserin- and placebo-treated groups in terms of any risk of adverse cardiovascular events, suggesting non-inferiority. However, it was found that more participants ( $n = 462$ ; 7.7%) treated with lorcaserin were diagnosed with cancer as compared to those treated with the placebo ( $n = 423$ ; 7.1%). Approximately 0.9% and 0.6% of patients died from cancer in the lorcaserin and placebo group, respectively. The number of participants diagnosed with a novel cancer was similar in both the lorcaserin ( $n = 76$ ) and placebo ( $n = 77$ )

groups within the first 180 days. However, in the next 180 to 900 days after randomization, the imbalance increased with longer duration of lorcaserin with greater than 1.0 point estimates for cancer rate ratios. Different types of cancer were diagnosed with a notably higher rate of colorectal, pancreatic, and lung cancer in the lorcaserin-treated group than in the placebo group [15].

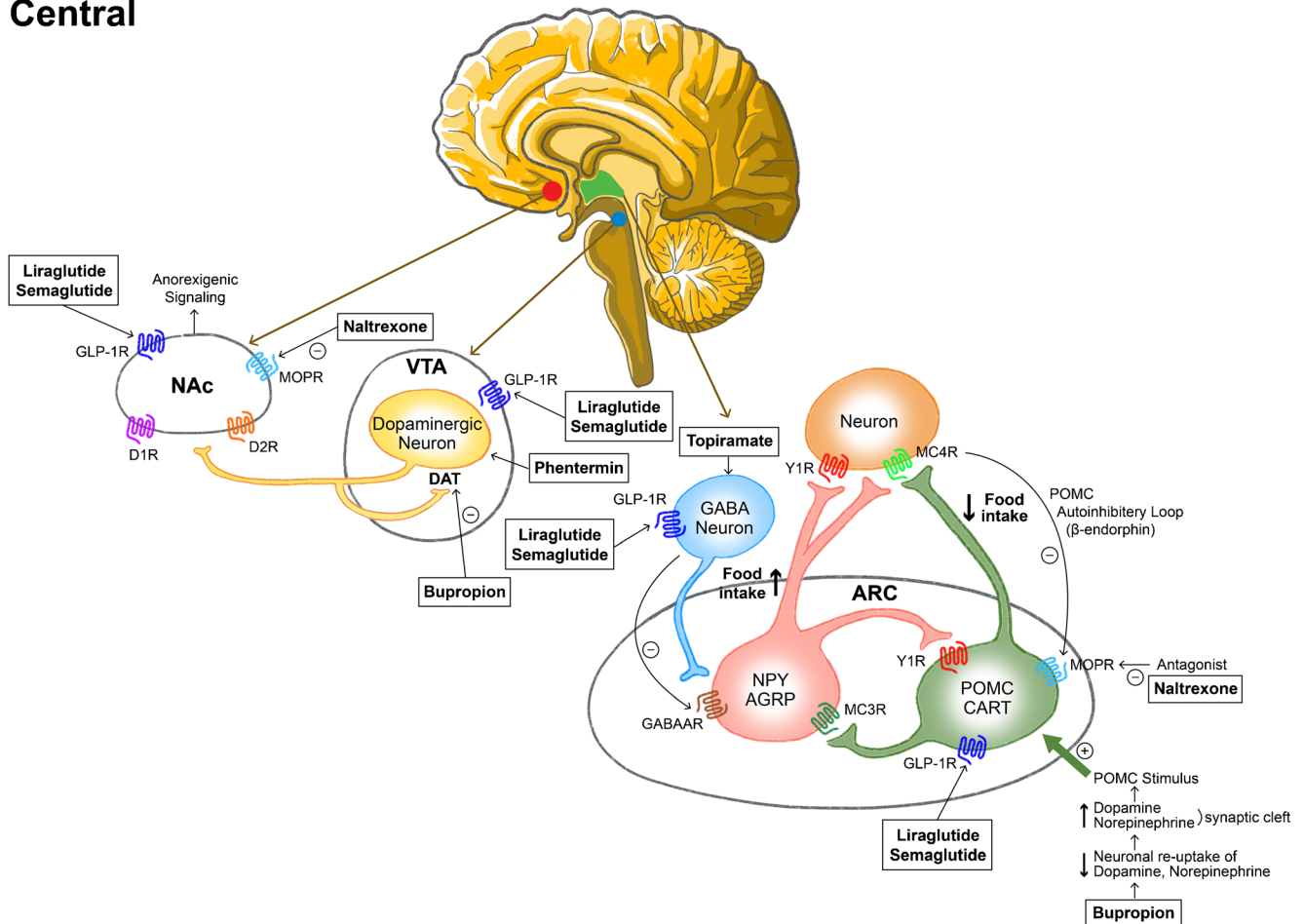
## Currently Approved Anti-Obesity Drugs for Long-Term Use

Figures 1 and 2 summarize the main mechanism of action for current anti-obesity drugs used to treat obesity (Table 1).

### Orlistat

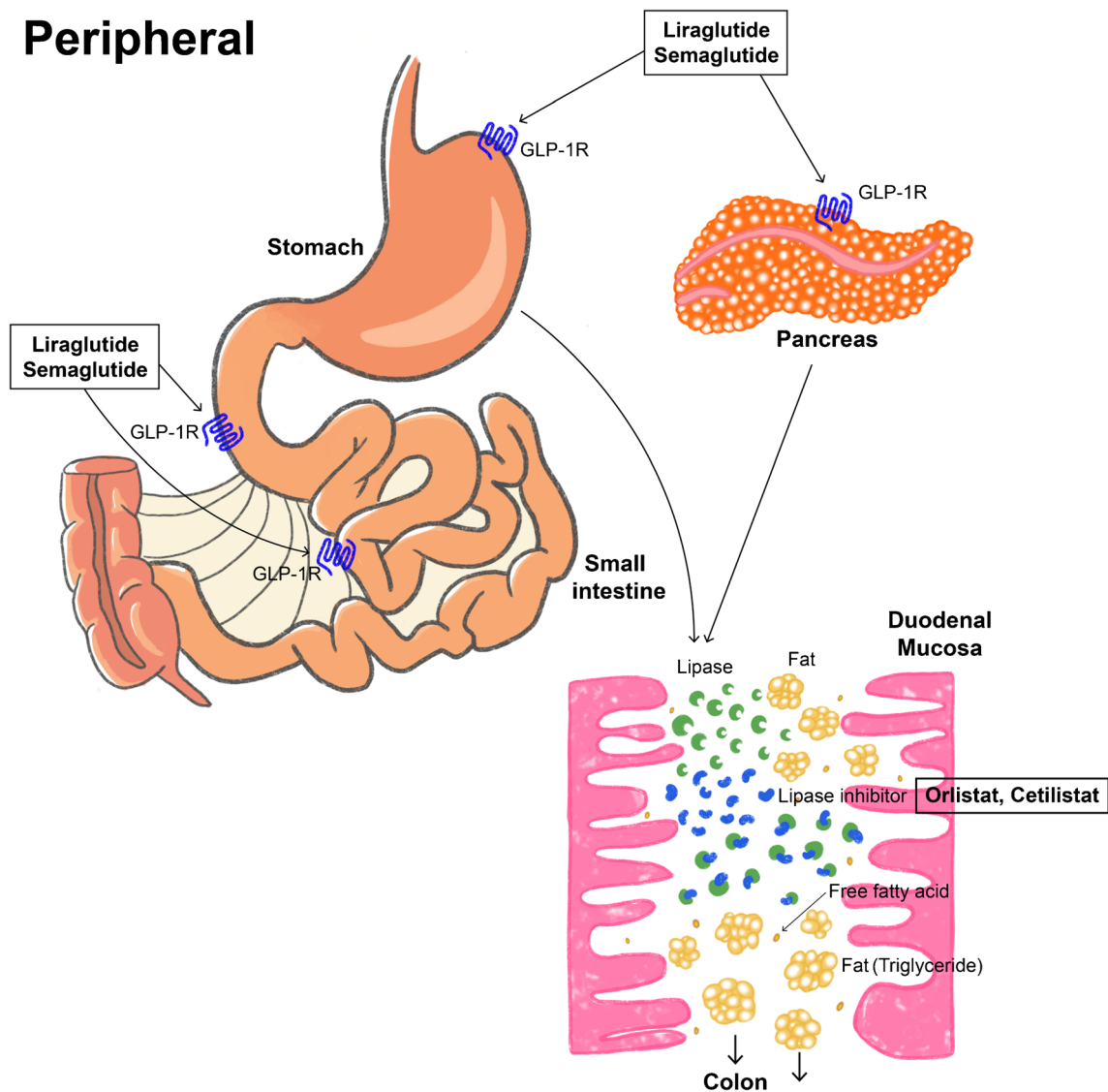
Orlistat (Xenical®), 120 mg, has been approved by the EMA and the FDA since 1998 and 1999, respectively, and its over the counter formulation of 60 mg (Alli®) is available in both

## Central



**Fig. 1** Central mechanisms of anti-obesity drugs. AGRP, agouti-related peptide; ARC, arcuate nucleus; CART, cocaine- and amphetamine-regulated transcript; DAT, dopamine active transporter; D1R, dopamine 1-class receptor; D2R, dopamine 2-class receptor; GABA, gamma-aminobutyric acid; GABAAR,  $\gamma$ -aminobutyric acid type A receptor;

GLP-1R, glucagon-like peptide-1 receptor; MC3R, melanocortin-3 receptor; MC4R, melanocortin-4 receptor; MOPR,  $\mu$ -opioid receptor; NAc, nucleus accumbens; NPY, neuropeptide Y; POMC, proopiomelanocortin; VTA, ventral tegmental area; Y1R, neuropeptide Y receptor type 1



**Fig. 2** Peripheral mechanisms of anti-obesity drugs. GLP-1R, glucagon-like peptide-1 receptor

the USA and Europe. As the longest licensed anti-obesity drug meant for long-term use, orlistat is prescribed for individuals  $\geq 12$  years of age [25]. Orlistat should be taken with meals or maximum 1 h after meals.

**Mechanism of Action** As a non-central nervous system agent, orlistat inhibits the action of gastrointestinal and pancreatic lipases, thereby blocking the hydrolysis of triglycerides and absorption of fatty acids carried out by the intestinal endothelium. This mechanism blocks the absorption of approximately one-third of the fatty acid consumed with food. As a result, it reduces calorie absorption without affecting the appetite [8]. Considering its mechanism of action, orlistat is more suitable for those who tend to eat fatty food and is expected to have greater weight-loss effects in them than in those with non-fatty food consumption habits.

**Side Effects** Orlistat is generally well tolerated; however, because of the non-absorbed fats in the intestine, patients can experience steatorrhea, frequent bowel movements, flatus with discharge, and fecal incontinence. By co-prescribing a fiber-containing supplement, such as psyllium, the gastrointestinal side effects of orlistat can be reduced. As orlistat prevents the lipid-soluble vitamins from being absorbed, vitamin A, D, E, and K supplements should be considered for long-term use.

**Clinical Efficacy** The efficacy of orlistat in promoting weight loss is modest with lifestyle modifications. In XENical for the prevention of diabetes in obese subjects (XENDOS) study, which was the largest randomized controlled trial (RCT,  $n = 3305$ ), orlistat caused a total body weight loss of 2.4% after 4 years. More importantly, it notably decreased the risk of T2DM in the drug-treated group (9.0%) as compared to the

**Table 1** A summary of anti-obesity drugs for long-term use

Drugs	Product name	Application	Mechanism of action	Main adverse effects	Contraindications	FDA approval	EMA approval
Orlistat	Xenical®, Alli®	60 or 120 mg TID during or within 1 h of a fat-containing meal	Gastrointestinal and pancreatic lipase inhibitor; decrease lipid absorption	Oily stools, oily spotting, fecal urgency, fecal incontinence, hyperdefecation, flatus with discharge, deficiency in vitamins A, D, E, and K	Pregnancy, cholestasis, malabsorption	Yes 1999	Yes 2012
Phentermine/topiramate	Qsymia®	3.75/23 mg QD for 14 days and then 7.5/46 mg QD; if < 3% weight loss is achieved at 12 weeks, increase to 11.25/69 mg QD for 14 days, followed by 15/92 mg QD; discontinue gradually if < 5% weight loss is achieved at 12 weeks with the highest dose	NE agonist/GABA agonist, glutamate antagonist; suppress appetite	Paresthesia, dry mouth, constipation, insomnia, dysgeusia, anxiety, depression	Pregnancy, uncontrolled HTN, CVD CKD, glaucoma, hyperthyroidism patients on MAOIs	Yes 2012	No
Naltrexon/bupropion	Contrave® Mysimba®	8/90 mg for 7 days; BID for 7 days; 2 tablets in the morning and 1 tablet in the evening for 7 days; and 2 tablets BID thereafter	Opioid receptor antagonist/-dopamine agonist and NE reuptake inhibitor; increase satiety, suppress appetite	Nausea, headache, constipation, dizziness, vomiting, dry mouth	Pregnancy, uncontrolled HTN, seizure, anorexia or bulimia nervosa, abrupt discontinuation of alcohol, benzodiazepines, barbiturates or antiepileptic drugs, other bupropion-containing drugs, opioids or opiate agonists, MAOIs	Yes 2014	Yes 2015
Liraglutide	Saxenda®	0.6 mg subcutaneous injection QD, increase by 0.6 mg weekly to a daily target dose of 3 mg	Glucagon-like peptide-1 agonist; slow gastric emptying, increase satiety, decrease food reward	Nausea, diarrhea, constipation, vomiting, dyspepsia	Pregnancy, personal or family history of medullary thyroid carcinoma or type 2 MEN	Yes 2014	Yes 2015

*BID*, twice daily; *CKD*, chronic kidney disease; *CVD*, cardiovascular disease; *EMA*: European Medicines Agency; *FDA*: Food and Drug Administration; *GABA*, gamma-aminobutyric acid; *HTN*, hypertension; *MAOI*, monoamine oxidase inhibitors; *MEN*, multiple endocrine neoplasia; *NE*, norepinephrine; *QD*, once daily; *TID*, three times per day; *XR*, extended-release

placebo-treated group (6.2%) [26]. Orlistat also lowered the blood pressure (BP), as well as improved insulin sensitivity and lipid profiles, as it reduces the absorption of intestinal fat. However, in this study, 91% of patients who received orlistat had at least one gastrointestinal issue and 8% withdrew from

the study due to adverse effects. Moreover, the potential risk of colorectal cancer remained due to the presence of excess fat in the colon. In animal studies, orlistat was associated with clusters of apoptosis-resistant, neoplastic, and premalignant colonic lesions [27]. In contrast, a previously conducted large

cohort study ( $n = 33,625$  with orlistat; 160,374 with placebo) showed no risk of colorectal cancer after the administration of orlistat [28].

### Phentermine/Topiramate

Phentermine/topiramate extended-release (ER) (Qysmia®) is the first combination agent for the long-term management of obesity that was approved by the FDA in 2012. However, the EMA has not approved this medication due to the lack of data on the cardiovascular effects of phentermine and its potential to induce addiction to the drug as well as the cognitive adverse effects (attention, language, and memory impairment) of topiramate on long-term usage of these drugs [29]. Since this drug combination contains phentermine, it is a controlled drug enforcement administration (DEA) schedule IV substance.

**Mechanism of Action** This drug combination mainly suppresses appetite through mechanisms that remain unclear. Since 1959, phentermine has been used for short-term weight control, which is allowed only for less than 12 weeks due to the lack of long-term safety data [30]. In animal studies, it has appetite-suppressant effects through interaction with biogenic amine transporters, which mainly enhances the norepinephrine as well as dopamine and serotonin release in the central nervous system (CNS) [31]. In rodents and humans, adrenergic, serotonergic, and dopaminergic neurons are spread throughout the CNS [10]. However, its mechanism of action in humans is not yet fully understood [32]. Topiramate, which acts as a glutamate antagonist, carbonic anhydrase inhibitor, and a gamma-aminobutyric acid agonist, is used for the treatment of epilepsy and prophylaxis of migraines [33]. Significant weight loss observed among epileptic patients who were prescribed topiramate led to the evaluation of the drug in clinical studies to find out its effect on obesity. Animal studies have suggested that topiramate boosts thermogenesis and acts as a neurostabilizer; however, the actions of topiramate on the CNS have not been completely understood [34, 35].

**Dose Escalation and Side Effects** Phentermine/topiramate is taken orally, once daily, in the morning to prevent insomnia. The dose of the drug is gradually escalated with a starting dose of 3.75/23 mg for 2 weeks, then 7.5/46 mg in the following weeks. A minimum of 3 months is needed before a further increase to the highest dose of 15/92 mg. Moreover, the dose is only increased if the patient fails to achieve a weight loss of at least 3% after 3 months of treatment. Unless weight reduction from the baseline is greater than 5%, the drug should be gradually discontinued [33]. In a previous study, it was found that patients with a history of seizures developed further seizures on discontinuing topiramate abruptly [14]. Therefore, if the patient is intolerant to the medication, a gradual titration

(over 3–5 days) is required to decrease the risk of seizures. The most common placebo-subtracted side effects of phentermine are paresthesia, dry mouth, dysgeusia, constipation, anxiety, depression, and insomnia, which are dose-dependent [36, 37]. Heart rate, electrolytes, and creatinine should be checked at the beginning of drug administration as well as periodically as the drug increases the heart rate (mostly small and transient), which might affect renal function and result in the development of metabolic acidosis and nephrolithiasis (because of carbonic anhydrase inhibition by topiramate) [31]. Contraindications observed are uncontrolled hypertension, CVD, chronic kidney disease, hyperthyroidism, glaucoma, and inhibition of monoamine oxidase within 14 days [33]. Fetal safety issue with a risk of oral clefts exists with this medication. Thus, advice on contraceptive planning is imperative before this medication is prescribed to women of child-bearing age.

**Clinical Efficacy** The three phase 3 RCTs (EQUIP, CONQUER, and SEQUEL, sponsored study name, not an acronym) demonstrated the efficacy of the medication [10–77]. EQUIP and CONQUER were 1-year randomized, double-blind, and placebo-controlled studies, including 1267 (non-diabetic patients with a BMI  $\geq 35$  kg/m<sup>2</sup>) and 2487 participants (BMI ranging from 27 to 45 kg/m<sup>2</sup> and more than two obesity-related comorbid conditions), respectively [36, 37]. In the EQUIP study, the mean weight reduction in patients after treatment with phentermine/topiramate ER (15/92 mg) for 1 year was 10.9%, while that after treatment with placebo was 1.6%. Similarly, in the CONQUER trial, patients administered with 7.5/46 mg and 15/92 mg of phentermine/topiramate ER for 1 year had a total body weight loss of 7.8% and 9.8%, respectively, as compared to the weight loss of 1.2% in patients administered with placebo. Thus, both studies showed a remarkable improvement in cardiovascular risk factors. Furthermore, the SEQUEL study, a 2-year extension trial, aimed at assessing the sustenance of weight loss in participants after completion of the CONQUER trial [38]. Weight loss was maintained over 2 years at 9.3% and 10.5% from the baseline for 7.5/46 and 15/92 mg doses of phentermine/topiramate ER, respectively [39]. The findings of this study reinforced previous results, which revealed that the drug can result in meaningful weight loss and favorable cardiovascular profile, including BP, lipid profiles, fasting glucose, fasting insulin, and waist circumference (WC). In a recent study, the occurrence of adverse cardiovascular events among the users of phentermine/topiramate ER was less frequent than the unexposed former users [40]. Meanwhile, a study that investigated the safety and efficacy of the drug used for the treatment of moderate-to-severe obstructive sleep apnea (OSA) in adults with obesity showed weight reduction as well as significant improvement in OSA as compared with the group treated with placebo. Additionally, phentermine/topiramate ER led to

improvement in other related parameters, such as respiratory disturbance index, apnea-hypopnea index (AHI), mean overnight oxygen saturation, and Pittsburgh Sleep Quality Index. More importantly, the reductions in body weight with the use of this medication showed a marked positive correlation with AHI [41].

### Naltrexone/Bupropion

Naltrexone/bupropion (Contrave®), a combination of drugs with two different mechanisms, is used for the long-term management of weight loss. Each component of this medication has been used for the treatment of other medical conditions since the 1980s [14]. The drug was approved by the FDA and EMA (Mysimba®) in 2014 and 2015, respectively. Since there is no evidence of any drug abuse induced by this medication, it is not a controlled substance.

**Mechanism of Action** One (naltrexone) of the two drugs has also been used as a monotherapy to treat addiction to alcohol, nicotine, and bupropion. As naltrexone is an opioid antagonist with a high affinity for the  $\mu$ -opioid receptor, it was approved for the treatment of opioid and alcohol addiction. It acts as an appetite-suppressant by disrupting  $\beta$ -endorphin-mediated POMC auto-inhibition [10]. Bupropion is an antidepressant and is mainly used to help in smoking cessation. Its anorectic mechanism of action involves the inhibition of dopamine and reuptake of norepinephrine. As naltrexone antagonizes an opioid-dependent feedback loop that limits the effects of bupropion on POMC neurons, this drug combination works synergistically [33, 42].

**Dose Escalation and Side Effects** To minimize the side effects, such as nausea, the dose of naltrexone/bupropion should be escalated gradually with a starting dose of one combination tablet (8/90 mg) every morning for 1 week, followed by one tablet BID in the morning and evening at week 2, two tablets in the morning and one tablet in the evening at week 3, and two tablets BID (the maximum dose) at week 4. Moderate nausea (21.9–24.5%), constipation (10%), vomiting (3.8–7.3%), dizziness (5.1–6.8%), dry mouth (5.5%), and headache (4.5–6.7%) have been reported to occur with the use of this drug [31]. Contraindications include uncontrolled hypertension, seizure, abrupt discontinuation of alcohol, anorexia or bulimia nervosa, benzodiazepines, use of barbiturates or anti-epileptic drugs, and inhibition of monoamine oxidase within the first 14 days of use of the drug. In addition, the patients administered with this drug should also be monitored for symptoms of depression or suicidal ideation. [29, 30].

**Clinical Efficacy** Four large clinical trials (Contrave Obesity Research (COR)-I ( $n = 1742$ ), COR-II ( $n = 1496$ ), the COR-intensive behavior modification study (COR-BMOD) ( $n =$

793), and COR-Diabetes ( $n = 505$ )) were conducted to assess the efficacy and safety of naltrexone/bupropion [42–45]. They included patients with a BMI  $\geq 27$  kg/m<sup>2</sup> and at least one weight-related comorbid condition, such as hypertension. The percent weight loss observed in patients taking 32/360 mg of naltrexone/bupropion for 56 weeks in COR-I, COR-II, and COR-BMOD as compared to those taking placebo in the same groups was 6.1 vs. 1.3%, 6.4 vs. 1.2%, and 9.3 vs. 5.1%, respectively [42–44]. The COR-DM trial included 505 patients with T2DM who were either overweight or obese [45]. Patients administered with 32/360 mg of naltrexone/bupropion for 56 weeks achieved a weight loss of 5.0% as compared to 1.8% in those administered with placebo. Additionally, it was observed that HbA1c reduction was greater ( $-0.6$  vs.  $-0.1\%$ ), the percentage of patients achieving HbA1c  $< 7\%$  was higher (44.1 vs. 26.3%), and there was an improvement in triglycerides and high-density lipoprotein-cholesterol in the naltrexone/bupropion-treated group as compared to those of the placebo-treated group. However, no difference was observed between both the groups in the incidence of depression, suicidal ideation, or hypoglycemia. Naltrexone/bupropion was associated with a higher incidence of nausea (42.3 vs. 7.1%), constipation (17.7 vs. 7.1%), and vomiting (18.3 vs. 3.6%) as compared with placebo [46].

### Liraglutide

Liraglutide (Victoza®) is a glucagon-like peptide 1 (GLP-1) agonist that was approved in 2010 for the treatment of T2DM; the recommended dose is subcutaneous (SC) administration of 1.8 mg daily [50]. The higher dose (3.0 mg SC daily) of liraglutide (Saxenda®) was approved by the FDA in 2014 and the EMA in 2015 for long-term weight management.

**Mechanism of Action** GLP-1 is secreted after meals from the distal ileum, proximal colon, and the vagal nucleus of the solitary tract, and it has multiple effects as an incretin hormone [32]. Its main role is to regulate blood glucose by inhibiting glucagon secretion and enhancing insulin secretion from the pancreatic  $\beta$ -cells in a glucose-dependent manner [31]. In addition, GLP-1 slows gastric emptying, induces postprandial satiety and fullness, and reduces appetite and food consumption by working on the hypothalamus, limbic/reward system, and cortex [33]. The pharmacodynamics of liraglutide is very complex, as it acts at different levels to maintain glucose homeostasis by regulating the survival of pancreatic  $\beta$ -cell, insulin secretion, and eating behavior [47]. Liraglutide is more stable in plasma and strongly binds to the plasma proteins, thereby having a longer half-life (13 h) than the human endogenous GLP-1 (a few minutes) [10].

**Dose Escalation and Side Effects** To prevent the side effects of nausea and vomiting, treatment with liraglutide should be

initiated with 0.6 mg QD and gradually increased by 0.6 mg up to 3 mg each week [30, 36]. Nausea (25.0%), vomiting (12.2%), diarrhea (11.6%), constipation (11.0%), and dyspepsia (6.4%) were frequently reported, which were tolerated by most patients over time [48–50]. However, a recent meta-analysis showed that among all the FDA-approved anti-obesity medications, liraglutide had the highest (13% of study participants) rate of discontinuation due to its side effects followed by naltrexone/bupropion (12% of study participants) [51]. Initially, there were concerns about the risk of acute pancreatitis; however, long-term trials reported that the risk does not notably increase with the use of liraglutide [52, 53]. Although the biomarkers, such as amylase and lipase, of acute pancreatitis rose in a non-dose-dependent manner during the treatment with GLP-1 receptor analogs, their increase was not accompanied by symptoms and acute pancreatitis was not diagnosed when monitored further [54]. However, studies on rodents revealed the proliferative effect of liraglutide on thyroid C-cells; thus, contraindications for liraglutide include individuals with (or with a family history of) medullary thyroid carcinoma or type 2 multiple endocrine neoplasia [29]. A phase 3b RCT showed no difference in the calcitonin levels and rate of medullary thyroid carcinoma between the placebo- and liraglutide-treated ( $\leq 1.8$  mg) groups, during a follow-up after 3.5 years [55]. Pancreatic, intestinal, and breast neoplasms were more frequently developed in rodents administered with incretin-based medications; however, these results were not confirmed in human studies [56–58]. However, the overall risk of malignant and benign neoplasms was higher in the liraglutide group than in the placebo group [52, 53, 59]. As these studies did not aim to investigate the risk of cancer or the incidence of medullary thyroid carcinoma, which had a very low incidence rate, the above results should be interpreted cautiously, and an intensive post-marketing surveillance of liraglutide should be performed. There have been no concerns reported regarding the neuropsychiatric safety; this medication can, thus, serve as an option for patients with obesity with mental disorders [60].

**Clinical Efficacy** Three main RCTs, The Satiety and Clinical Adiposity – Liraglutide Evidence (SCALE) Obesity and Prediabetes, SCALE Diabetes, and SCALE Maintenance [49, 61, 62], assessed the efficacy and safety of liraglutide. In the SCALE obesity and prediabetes cohort, including 61.2% of prediabetic participants, obese participants ( $n = 2487$ ) were administered with 3 mg QD of liraglutide or placebo. After 56 weeks, a weight loss of 8.0% was achieved in the liraglutide group as compared to 2.6% in the placebo group. In addition, weight reduction  $\geq 5\%$  and  $\geq 10\%$  was achieved by 63.2% and 33.1% of the participants in the liraglutide group, respectively, as well as by 27.1% and 10.6% in the placebo group, respectively [49]. Moreover, BP, lipid profiles, HbA1c ( $-0.30\% \pm 0.28$ ), and fasting

glucose levels ( $-7.1$  mg/dL  $\pm 0.8$ ) improved in the liraglutide group as compared to those in placebo group. The SCALE Diabetes assigned diabetic patients with obesity ( $n = 846$ ) to receive 3 mg, 1.8 mg QD of liraglutide, or placebo for 56 weeks and reported weight reduction in the patients (6.0%, 4.7%, and 2.0%, respectively) [49]. Early weight reduction  $\geq 4\%$  was associated with greater weight loss with 3 mg of liraglutide (at 16 weeks) at the end of the study [63]. Compared to the 1.8 mg group, the 3.0 mg group had a greater improvement in HbA1c, fasting plasma glucose, Homeostatic Model Assessment for Insulin Resistance, and the number of hypoglycemic agents. The SCALE Maintenance was designed to assess weight maintenance in non-diabetic participants who underwent a  $\geq 4$ -week run-in with a low-calorie diet. Subjects ( $n = 422$ ) who lost 5% or more of the initial body weight were assigned to the liraglutide 3.0 mg or placebo group for 56 weeks. Liraglutide group (3.0 mg) achieved an additional weight reduction of 6.2% as compared to 0.2% in placebo group [62]. Compared with other anti-obesity drugs, one of the main benefits of liraglutide is that it does not contribute to the incidence of CVD in obese patients with T2DM [64].

## New Drugs Under Development

Various obesity drugs, including obesity vaccines, are under development. However, the results of human clinical studies on anti-obesity drug candidates have not yet been published, or, unlike in vitro or animal studies, no actual weight loss was observed, or were abandoned in the middle due to serious side effects are not covered here.

## Semaglutide

Semaglutide is a long-acting GLP-1 analog that can be administered once a week, while liraglutide is a short-acting GLP-1 analog that should be administered daily. Semaglutide, similar to liraglutide, was recently approved in Europe, Japan, and North America as a treatment for T2DM. Semaglutide not only regulates blood sugar similar to native GLP-1 but also plays a role in reducing energy intake, increasing satiety, and reducing hunger. In a previous study, administration of 1 mg of semaglutide once every week for 12 weeks resulted in a weight loss of 5 kg, decreased appetite and food cravings, better controlled diet, and reduced preference for fatty or energy-rich foods [65]. In another study conducted by the same research team, a 12-week semaglutide, placebo cross-over test was conducted in 30 obese patients. In the group administered with semaglutide once a week (with gradual escalation to 1 mg per week), both glucose and lipid metabolism (fasting and after meals) as well as the first-hour gastric emptying time was delayed [66]. In addition, a phase 2 clinical study, conducted for 52 weeks, revealed the long-term effects



of semaglutide on weight loss in adults with obesity. A total of 957 patients with an average age of 47 years and a BMI of 39.3 kg/m<sup>2</sup> were randomly assigned to three groups: first group was administered with final doses of 0.05, 0.1, 0.2, 0.3, and 0.4 mg of liraglutide (injected subcutaneously once daily); second group was administered with 3 mg of liraglutide (injected subcutaneously once daily); and third group was administered with placebo. The semaglutide was increased by 0.05 mg after 4 weeks and by 0.1 mg every 4 weeks thereafter. In addition, among the final semaglutide groups that were administered with final doses of 0.3 and 0.4 mg, a group was assigned that started from 0.05 mg and increased rapidly every 2 weeks. The liraglutide administration group increased 0.6 mg every week from 0.6 to 3.0 mg. The estimated mean weight loss after 52 weeks was 2.3% in the placebo group, compared to 6.0%, 8.6%, 11.6%, 11.2%, 13.8%, and 7.8% for the final doses of 0.05, 0.1, 0.2, 0.3, 0.4 mg, and 3 mg liraglutide, respectively. The rate of weight loss of  $\geq 10\%$  was 10% in the placebo group as compared to 37–65% in the group administered with 0.1 mg or more of semaglutide ( $P < 0.0001$ ). Overall, the semaglutide-treated group tolerated well, and there were no new side effects other than gastrointestinal symptoms, such as nausea, which is known as the most common side effect of liraglutide [66]. Five semaglutide treatment effects in people with obesity (STEP) programs, a phase 3 clinical study on weight loss and safety of administering semaglutide once weekly, are currently being studied as follows: STEP 1, weight loss; STEP 2, weight loss in T2DM; STEP 3, weight loss in combination with intensive behavioral therapy; STEP 4 for sustained weight maintenance; and STEP 5 for long-term weight maintenance. The study subjects of STEP 2 were T2DM patients with a BMI of 27 kg/m<sup>2</sup> or higher, and all others were patients with obesity having a BMI of 30 kg/m<sup>2</sup> or higher or BMI 27 kg/m<sup>2</sup> or higher with obesity-related complications. STEP 1–4, a study with a 68-week administration period, is expected to end by 2020, whereas STEP 5, which is a 104-week administration period, is expected to be completed in 2021 [67].

### Gastric Inhibitory Polypeptide and GLP-1

GLP-1 is secreted from L cells located in the lower small intestine and colon, GIP from K cells located in the proximal small intestine, and glucagon from  $\alpha$ -cells of the pancreatic islets of Langerhans. GLP-1 suppresses appetite and reduces energy intake, while GIP has no effect on dietary behavior. Nevertheless, when GLP-1 and GIP are administered together, interestingly, since GIP enhances the satiety-inducing effect of GLP-1, a novel dual GIP-1 receptor (GLP-1R)/GIP receptor (GIPR) agonist has the potential to be a new obesity treatment. However, contrary to expectations, the clinical results were different from the theory. Seventeen overweight or obese

males were given either GIP or GLP-1 alone for 5 days, or GIP+GLP-1 at the same time, and allowed to eat ad libitum food 240 min later, and there was no effect on energy intake in the GIP group. Energy intake decreased in the GLP-1 administration group, but energy intake increased more in the GIP+GLP-1 combination administration group ( $P = 0.039$ ) [68].

### Combined GLP-1, Oxyntomodulin, and Peptide YY

Oxyntomodulin (OXM) is a natural 37 amino acid peptide that is released from the oxyntic (fundic) cells of the oxyntic (fundic) mucosa of the colon in the post-prandial state. It has a role as a dual GLP1R/glucagon receptor (GCGR) agonist, resulting in suppressed appetite and increased energy expenditure in humans. GOP refers to a solution in which GLP-1 (7–36), OXM, and peptide YY (PYY) (3–36) are mixed. In this single-blinded mechanistic study, 26 obese patients with prediabetes/diabetes were randomly infused with GOP ( $n = 15$ ) or saline ( $n = 11$ ) for 4 weeks. After 4 weeks, the GOP group lost an average of 4.4 kg (95% CI,  $-5.3$ – $-3.5$  kg), which was more weight loss compared to 2.2 kg (95% CI,  $-4.1$ – $-0.9$  kg) of the placebo group ( $P = 0.025$ ) [69]. In another study, during 10.5 h of GOP or saline infusion, colonists were asked to eat ad libitum for lunch and dinner, resulting in a 32% reduction in food intake in the GOP group compared to the control group [70]. However, no clinical studies have yet been performed to verify the long-term weight loss effect of GOP.

### Dual GLP-1R/Glucose-Dependent Insulinotropic Polypeptide Receptor Agonist, GLP-1R/GCGR Agonists

GLP-1R agonists potentiate glucose-induced insulin secretion (GIIS) from pancreatic  $\beta$ -cells, which potently stimulates insulin secretion and enhances insulin sensitivity in adipose tissue, via enhanced  $\beta$ -cell activity of GIPR. Here, we briefly introduce new drugs under development with the results of clinical phase 2 studies.

#### GLP-1R/GIPR Agonist

##### LY3298176 (Tirzepatide; Eli Lilly), Dual GLP-1R/GIPR Agonist

LY3298176 is a novel dual GLP-1R/GIPR agonist under development as a treatment for T2DM. In a 26-week randomized phase 2 study, a total of 318 T2DM patients with a BMI of 23–50 kg/m<sup>2</sup> were randomly assigned to the once-weekly subcutaneous LY3298176 (1 mg, 5 mg, 10 mg, or 15 mg), dulaglutide (1.5 mg), or placebo group [71]. After 26 weeks, the average weight loss of the LY3298176 group, the dulaglutide group, and the placebo group were  $-0.9$ – $-11.3$  kg,  $-2.7$  kg, and  $-0.4$  kg, respectively. At 26 weeks, proportion of participants who had weight reduction over 5% (10%) of initial body weight was 14–71% (6–39%), 22%

(9%), and 0% (0%), respectively, in the LY3298176 group, the dulaglutide group, and the placebo group. The average WC reduction in the LY3298176 group, the dulaglutide group, and the placebo group were  $-2.1$ ,  $-10.2$  cm,  $-2.5$  cm, and  $0.13$  cm, respectively. Side effects were reported in 4%, and gastrointestinal events (nausea, diarrhea, and vomiting) were the most common side effects and were dose-related. Most were minor-moderate and temporary. Second, decreased appetite was common.

## GLP-1R/GCGR Agonists

### SAR425899 (Sanifi), Dual GLP-1R/GCGR Agonists

There are two randomized, placebo-controlled, double-blind clinical trials for subcutaneous injection of SAR425899 [72]. In one study, 32 healthy overweight (BMI 25–30 kg/m<sup>2</sup>) volunteers were given single-ascending doses (0.01–0.1 mg) of SAR425899 or placebo, and in another study, 40 healthy normal-to overweight volunteers (BMI 20–30 kg/m<sup>2</sup>) and 36 T2DM patients with a BMI of 28–42 kg/m<sup>2</sup> were given a multiple-ascending-dose of SAR425899 or placebo daily for 21 or 28 days. As a result, SAR425899 lowered fasting blood glucose and glycated hemoglobin in T2DM patients, and reduced weight by up to 5.32 kg in healthy volunteers and 5.46 kg in T2DM patients. No clinical studies have yet been performed to verify the long-term weight loss effect of SAR425899.

### MEDI0382 (Cotadutide; AstraZeneca), Dual GLP-1R/GCGR Agonists

In a randomized, placebo-controlled, double-blind, combined multiple-ascending dose and phase 2a study, T2DM patients (glycated hemoglobin A1c 6.5–8.5%) with a BMI of 25–40 kg/m<sup>2</sup> between 18 and 65 years old were randomly administered MEDI0382 or placebo up to 300 µg daily for 22 days or 200 µg for 41 days [73]. The body weight in the MEDI0382-treated group was 3.84 kg (90% CI,  $-4.55$ – $-3.12$  kg), which was significantly lower than 1.70 kg (90% CI,  $-4.55$ – $-3.12$  kg) in the placebo group ( $P=0.0008$ ). Gastrointestinal disease and loss of appetite were more frequent in the MEDI0382 group than in the placebo group.

### Cetilistat

In 2013, cetilistat, a pancreatic lipase inhibitor, was approved as a treatment for obesity in Japan, which was marketed as Oblean® by Takeda. It has a role in the same way as orlistat by inhibiting pancreatic lipase, an enzyme that hydrolyzes triglycerides into absorbable free fatty acids in the intestine. The recommended dose was 120 mg three times a day immediately after each meal. A 12-week, multicenter, randomized,

double-blind, phase 2 clinical trial was conducted in obese patients with diabetes. The cetilistat group lost 3.85–4.32 kg, similar to the 3.78 kg weight loss of the orlistat group [74]. Glycosylated hemoglobin was also reduced. Its side effects were similar to those of the orlistat group and were well tolerated. However, there are no studies on the long-term effects of cetilistat on weight loss and safety.

### Triple Monoamine Reuptake Inhibitors, Tesofensine (NS-2330)

Tesofensine (also known as NS-2330) is a novel triple monoamine reuptake inhibitor with intrinsic inhibitory activity on norepinephrine, serotonin, and dopamine transporter function. Its appetite suppression and energy consumption-increasing effects have been confirmed; therefore, it is expected to be an obesity treatment [75]. A 24-week, multicenter, randomized, double-blind, phase 2 clinical trial was conducted in 203 obese patients with a BMI of 30–40 kg/m<sup>2</sup>, in combination with an energy-restricted diet. The mean weight loss after 24 weeks was 2.5% in the placebo group, but 4.5%, 9.2%, and 10.6% in the tesofensine 0.25 mg, 0.5 mg, and 1.0 mg groups, respectively ( $P<0.0001$ ). The most common side effects were dry mouth, nausea, constipation, hard stools, diarrhea, and insomnia. In the tesofensine 0.5 mg group, the pulse rate increased 7.4 times per minute after 24 weeks, but there was no increase in BP [76]. The results of a phase 3 study of tesofensine have not been reported.

### GOAT Inhibitors

Ghrelin, known as the hunger hormone, is produced by the peripheral organs and acts to centrally stimulate the appetite [78]. Two major forms of ghrelin exist in circulation: acylated ghrelin (AG) which is active form of circulating ghrelin and unacylated ghrelin (UAG). Ghrelin O-acyl transferase (GOAT) has been considered the main enzyme responsible for acylation of ghrelin, and emerging as an important molecule in treating obesity [79]. In preclinical studies, treatment with GOAT inhibitor resulted in decreased food intake [77, 80].

Recently, GLWL Research Inc. (Montreal, QC, Canada) has completed a phase 2 trial to evaluate the efficacy, safety, and pharmacokinetics of GLWL 01 (orally available GOAT inhibitor) for treating hyperphagia in patients with Prader-Willi syndrome (PWS) (aged 16–65 years) (NCT03274856) [81].

### Leptin

Leptin, produced by adipocytes, was initially considered a potential target for development in anti-obesity medication as early animal studies showed the linkage between leptin

deficiency and severe obesity [11]. However, on the contrary, human study showed that patients with obesity were leptin-resistant and had higher levels of leptin [82]. Currently, mechanisms to improve leptin resistance through combination therapy have been explored. Metreleptin (Myalept) is an injectable human recombinant leptin analogue and approved in Japan and the USA for the treatment of complications of leptin deficiency in patients with congenital or acquired generalized lipodystrophy [83]. Human studies including children have demonstrated the effect of Metreleptin on improving hyperglycemia, hypertriglyceridemia, and hepatic fatty steatosis in patients with lipodystrophy characterized by congenital or acquired loss of adipose tissue [84, 85]. Anti-metreleptin antibodies with neutralizing activity have been identified in patients treated with metreleptin [86]. The consequences are not well characterized due to the small number of reports however, could include inhibition of endogenous leptin action resulting in loss of the drug efficacy. Regardless of treatment with metreleptin, T cell lymphoma has been reported in patients with acquired generalized lipodystrophy. Because of these, metreleptin is not indicated for use in patients with general obesity without concurrent evidence of generalized lipodystrophy or those with HIV-related lipodystrophy [87].

#### **Amylin Analogues and Dual Amylin/Calcitonin Receptor Agonists**

Amylin secreted by pancreatic  $\beta$ -cells acts to reduce postprandial glucagon secretion, slow gastric emptying, and centrally increase satiety [88]. Pramlintide, amylin analogue, was licensed by the FDA in 2005 for diabetic patients. Early studies showed that pramlintide use in patients with insulin-treated diabetes improved glycemic control and supported weight reduction by decreasing food intake [89]. A subsequent study of pramlintide demonstrated an additional mean weight loss of 3.7 kg vs. placebo in obese patients without T2DM or with non-insulin-treated T2DM [89]. While pramlintide monotherapy resulted in 1.5 kg additional weight loss compared with placebo over 24 weeks, combination of pramlintide with either phentermine or sibutramine resulted in 9.2 kg weight loss [90]. Davalintide, a second-generation amylin analogue, was developed and completed phase II trials. However, weight reduction with the drug were disappointing causing discontinuation in its development [91]. As the human amylin receptor consists of calcitonin receptor with activity-modifying proteins amylin analogues in combination with calcitonin receptor agonists, known as dual action amylin and calcitonin receptor agonists, are novel anti-obesity agent targets of study [92]. While animal studies (KBP-042, KBP-089) showed anti-obesity effect [93, 94], human clinical trials are still awaited.

#### **Setmelanotide**

Setmelanotide (also known as RM-493) is a potent and selective melanocortin-4 receptor (MC4R) agonist [95]. The activation of MC4R, a seven-transmembrane domain G protein-coupled receptor, inhibits food intake and stimulates energy expenditure, leading a negative energy balance and potentially weight reduction. With high affinity to the human MC4R, setmelanotide activates MC4R efficiently and has potential in resolving obesity [96, 97]. In a phase 2, randomized, double-blind, placebo-controlled pilot study to evaluate the effects of a once daily subcutaneous injectable formulation of setmelanotide (NCT02311673), 40 patients with Prader-Willi syndrome (PWS) (aged 16–65 years) treated with the highest dose achieved clinically meaningful weight reduction despite modest improvement in hyperphagia [98].

#### **Sodium-Glucose Co-Transporter-2 Inhibitors**

SGLT-2 inhibitors, such as dapagliflozin, empagliflozin, and canagliflozin, block glucose reabsorption from the renal tubules and result in glycosuria (energy deficit). Previous RCTs reported that selective SGLT2 inhibitors, a new class of anti-diabetes drugs, have been shown to reduce body weight (1–3 kg reduction) in diabetic patients with and without obesity [99–102]. In previous clinical trials that examined SGLT2 inhibitors in combination with phentermine, additional weight loss was achieved (6.9%, canagliflozin 300 mg + phentermine 15 mg vs. 1.3%, canagliflozin 300 mg vs. 3.5%, phentermine 15 mg) [103, 104]. Similarly, SGLT-2 inhibitors combined with a GLP-1 agonist caused a greater weight reduction than individual administration of each agent [105, 106]. In addition, it has been reported that by inhibiting SGLT-1, expressed in the small intestine, absorption of intestinal glucose and galactose decreases, while GLP-1 and PYY increase. Recent RCTs demonstrated that licogliflozin, a dual SGLT1/2 inhibitor, significantly reduced body weight by 5.7% over 12 weeks and 3.8% over 24 weeks in obese patients (BMI, 35–50 kg/m<sup>2</sup>) with or without diabetes. Diarrhea occurred in 90% who received licogliflozin [107, 108].

#### **Leucine-Metformin-Sildenafil Combination**

AMP-activated protein kinase (AMPK) and mammalian sirtuin 1 (Sirt1) are regulators of lipid and energy metabolism that inhibit fat accumulation and stimulate fatty acid oxidation via reciprocal activation [109]. L-leucine is known as an allosteric activator of Sirt1 and metformin is a synergistic coactivator of sirtuin pathway signaling. Sirt1 also is stimulated by nitric oxide (NO), which is enhanced through sildenafil, a phosphodiesterase type 5 inhibitor. A phase 2 RCTs demonstrated that body weight was significantly reduced in overweight or obese patients with a BMI ranging from 25 to

**Table 2** Data from meta-analyses of the anti-obesity drugs approved for long-term use for weight loss

Drugs	Study (duration $\geq 1$ year)	Subjects (drug/placebo)	Lifestyle intervention (diet/exercise/behavior)	Weighted mean difference (kg) (95% CI) for the drug-to-placebo comparison at 1 year	% weight loss (drug/placebo) (95% CI)	Odds ratio (95% CI) for achieving $\geq 5\%$ weight loss at 1 year (drug, placebo)	% of patients with $\geq 10\%$ weight loss at 1 year (drug, placebo)	Odds ratio (95% CI) for discontinuation due to adverse events
Orlistat	17 trials	5572/5572	Reduced fat intake or 500–800 kcal deficit/non-specific increase or 30 min of moderate exercise per day/yes or no	2.60 (2.16–3.04)	4.6/1.7	2.70 (2.34–3.09)	48.8/22.6	1.84 (1.53–2.21)
Phentermine/topiramate	3 trials	1802/1735	500 kcal deficit/non-specific increase/yes	8.80 (7.42–10.2)	8.5/1.7	9.22 (6.63–12.85)	72.0/22.8	2.29 (1.71–3.06)
Naltrexone/bupropion	5 trials	6963/5897	500 kcal deficit/non-specific increase or 30 min of moderate exercise per day/yes	4.95 (3.96–5.94)	6.1/2.1	3.96 (3.03–5.11)	52.4/28.3	2.64 (2.10–3.35)
Liraglutide	4 trials	3096/1649	500 kcal deficit/minimum 150 min of brisk walking per week/yes	5.27 (4.52–6.06)	7.1/1.7	5.54 (4.16–7.78)	60.3/24.6	2.95 (2.11–4.23)

CI, confidence interval; *CrI*, credible interval

40 kg/m<sup>2</sup> ( $n = 32$ ) to receive a fixed-dose combination of leucine 1.1 g, metformin 0.5 g, and sildenafil 1.0 mg for 16 weeks [110].

### The Limits and Challenges of Obesity Treatment with Anti-Obesity Drugs

Given the high prevalence and severity of obesity endemic, there are many fewer therapeutic options for weight control medication than those for other chronic diseases such as hypertension, T2DM, and dyslipidemia. Despite a lot of evidence demonstrating significant weight loss effects and safety of pharmacotherapy, and many guidelines emphasize the importance of anti-obesity medications for patients who fail to lose weight with lifestyle modification; these medications are still underused [8, 111]. Fewer than 2% of obese patients have been treated with anti-obesity drugs in the United States [112]. One of the main reasons for the under-prescription of anti-obesity drugs is the side effects. Since obesity develops via multifactorial pathways, a single drug might exhibit limited efficacy. Thus, a high dose is often required, which often causes unacceptable side effects. The majority of side effects of anti-obesity drugs are dose-dependent. Therefore, combination therapy consisting of multiple anti-obesity drugs with complementary modes of action is warranted to broaden the target energy regulatory systems and maximize the effect on weight management while maintaining safety and tolerability [113]. Meanwhile, current anti-obesity drugs approved for chronic weight loss generally have favorable effects on cardio-metabolic parameters. However, the long-term safety of orlistat, naltrexone/bupropion, and phentermine/topiramate on cardiovascular morbidity and mortality have not been established [114]. In addition, obesity has long been stigmatized as an individual's problem caused by laziness or greedy eating habits [112]. Thus, many patients with obesity are reluctant to discuss their body weight with doctors because they feel ashamed or helpless to seek care for it [103]. Physicians may also be too busy to address the weight problems of their patients and consider it more efficient to treat obesity-related comorbidities [115, 116]. Weight loss is extremely challenging to achieve and sustain, and long-term management of obesity often requires adjunctive pharmacological interventions. The high cost of long-term use of these medications also prevents adequate prescription. In many clinical trials that assessed pharmacologic interventions for more than 12 months, a weight loss of 4 to 8% was typical [51], which is rather disappointing considering the high prices of these drugs. Furthermore, once drug therapy is discontinued, weight reduction is not generally sustained; thus, adherence and persistence with the medication are essential determinants of real-clinical strategies for weight control [117]. In a recent study investigating persistence with anti-obesity medications, liraglutide 3.0 mg had significantly lowest risk of

discontinuation compared to lorcaserin (HR = 0.46), naltrexone/bupropion (HR = 0.48), and phentermine/topiramate (HR = 0.64) (mean follow-up duration of 342–427 days). Male sex, older age, concomitant hyperlipidemia, and never phentermine users were associated with higher persistence [118]. As a result, the decision to initiate drug therapy in an obese individual should be made after the risks and benefits are considered. Importantly, health providers should determine the risk-benefit profile of a given anti-obesity drug on a patient-by-patient basis. Furthermore, the treatment goals should be clear. Patient preferences based on tolerability markedly affect adherence and can cause poor adherence or discontinuation, thereby negating the treatment effects [119, 120]. The goal of treatment with anti-obesity drugs in obese individuals should be long-term maintenance of weight reduction and improvement in overall health.

### Conclusion

Obesity, similar to hypertension and diabetes, is a chronic progressive disease, resulting from multiple environmental and genetic factors that require lifelong management. In case of hypertension and diabetes, drugs are used if BP and blood sugar levels are not controlled by adequate therapeutic lifestyle changes. If BP and blood sugar are properly controlled with drugs without any serious side effects, the drugs are administered continuously. Anti-obesity drugs should be treated in similar manner. However, obese patients as well as some doctors are still reluctant to continue using anti-obesity drugs. Through this review along with safety data, we looked at drugs with long-term usage that reduce weight and improve comorbid diseases or conditions in patients with obesity. As the morbidity and mortality of obesity have significantly increased, pharmacological treatment should be considered as part of a comprehensive strategy for the treatment of patients with a BMI  $\geq 30$  or  $\geq 27$  kg/m<sup>2</sup> and an obesity-related comorbidity. Data from the most recent meta-analyses showed that the overall placebo-subtracted weight reduction (%) with the use of anti-obesity drugs for at least 12 months ranged from 2.9 to 6.8%: phentermine/topiramate (3 trials, 6.8%) liraglutide (4 trials, 5.4%), naltrexone/bupropion (5 trials, 4.0%), and orlistat (17 trials, 2.9%) [11, 54, 81–84] (Table 2). Most of the previous trials conducted on these drugs also controlled diet and exercise in both the placebo and treatment groups. Thus, these medications were proposed for use as pharmacotherapy in conjunction with healthy eating, physical activity, and behavioral modification. It is necessary to select these anti-obesity drugs that have proven long-term effectiveness and are safe. In addition, physicians should continue to follow-up on the problems and prognosis of patients with obesity.

## Compliance with Ethical Standards

**Conflict of Interest** The authors declare that they have no conflicts of interest.

**Human and Animal Rights and Informed Consent** This article does not contain any studies involving human or animal subjects performed by any of the authors.

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