

Review Article

Metabolic syndrome and related conditions

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Anti-Obesity Drugs: Long-Term Efficacy and Safety: An Updated Review

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As a chronic and relapsing disease, obesity negatively impacts the health of men to a greater extent than that of women, with a higher risk of cardiovascular disease. Since lifestyle modifications alone are often challenging and limited for the maintenance of weight reduction, pharmacotherapy should be considered in a timely manner for obese men or overweight patients with weight-related comorbidities. Recent advances in anti-obesity drugs have enabled the potential of achieving clinically significant weight loss. Increasing evidence has shown that behavior-based interventions with one of these medications can result in greater weight loss than that elicited by usual care conditions. Data from most recent meta-analyses showed that the overall placebo-subtracted weight reduction (%) with the use of anti-obesity drugs for at least 12 months ranges from 2.9% to 6.8%; phentermine/topiramate (-6.8%) liraglutide (-5.4%), naltrexone/bupropion (-4.0%), lorcaserin (-3.1%), and orlistat (-2.9%). However, they have a high cost and may cause adverse outcomes depending on the individual. Very recently, on February 13, 2020, the US Food and Drug Administration requested withdrawal of lorcaserin from the market because a safety clinical trial showed an increased occurrence of cancer. Therefore the decision to initiate drug therapy in obese individuals should be made after the benefits and risks are considered. Thereafter, treatment should be tailored to specific patient subpopulations depending on their chronic conditions, comorbidities, and preferences. Herein, we provide an overview of the latest developments in weight loss medications, which may serve as one of the strategies for long-term obesity control.

Keywords: Liraglutide; Lorcaserin; Naltrexone/bupropion; Obesity; Orlistat; Phentermine/topiramate

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INTRODUCTION

Recently, the “epidemic of obesity” has emerged as one of the major global health concerns. Between 1975 and 2016, the worldwide prevalence of obesity tripled and was primarily attributed to the intake of a high calorie diet and a sedentary lifestyle [1]. Although the prevalence of being overweight was similar between

men (39%) and women (40%) in 2016 according to the World Health Organization, recent studies have reported more rapid increases in obesity-related indicators in men than in women [2,3]. This sex disparity can be explained by genetic, sociocultural, socioeconomic, and behavioral factors [4]. After starting a career, men might succumb to obesogenic environmental changes—frequent dining outside the home, drinking, and stress,

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which ultimately lead to high calorie intake [3]. Men also tend to have lower body image dissatisfaction than women. Resultantly, they tend to be less interested in the weight gained over time than women [5].

Excess fat distribution displays different patterns according to gender; it is concentrated in the centrally located visceral areas in men and subcutaneous areas in premenopausal women [6]. This difference may explain the greater negative impact of obesity on the cardiovascular health of men than on that of premenopausal women. Unlike subcutaneous fat, visceral fat is related to the worsening of insulin resistance and lipid and fluid metabolism [4]. Additionally, obesity in men predominantly reduces total testosterone due to the insulin resistance-associated decrease in sex hormone-binding globulin. Severe obesity is also related to reductions in free testosterone levels *via* suppression of the hypothalamic–pituitary–thyroid axis, whereas low testosterone alone results in increases in adiposity, thereby establishing a self-perpetuating cycle of metabolic impairment [7,8]. Previously, obese men were found to have a greater risk of erectile dysfunction (ED). In fact, obesity can cause vasculogenic ED, which has common features, including obesity-related metabolic alterations [9].

Timely and appropriate treatment to reduce excessive body fat is required in men with a body mass index (BMI) ≥ 30 kg/m² (25 kg/m² for some ethnic groups), ≥ 27 kg/m² (23 kg/m² for some ethnic groups) and obesity-related comorbidities or abdominal obesity (waist circumference [WC] ≥ 102 cm [90 cm for some ethnic groups]) [10,11]. Although intensive lifestyle modification, including calorie restriction and engaging in physical activities, is the first approach to ameliorate obesity, sustaining these efforts over a long period can be challenging and often prove insufficient [12]. Currently, most guidelines recommend pharmacotherapy as a second-line treatment for weight management after lifestyle modification [13,14]. In fact, numerous medications have been developed for the long-term management of obesity, with different mechanisms targeting various factors and diverse pathways that might cause a positive energy balance [15]. During the last decades, some anti-obesity drugs have been used to treat morbid obesity; however, most of these have been removed from the market owing to serious long-term side effects, particularly cardiovascular-related issues [16]. Since then, efforts to develop anti-obesity

drugs have been made focusing on not only weight loss efficacy but also cardiovascular safety and lowered risk of cardiovascular disease (CVD). In recent years, the US Food and Drug Administration (FDA) has approved newer pharmacological options following more cautious studies elucidate their safety and efficacy [17]. 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 [18]. Importantly, the availability of different medications offers healthcare providers more options for deriving better patient-tailored treatment plans. In this review, we aimed to provide an overview of the latest developments in weight loss medications, which may serve as one of the strategies for long-term obesity control (Table 1).

ANTI-OBESITY DRUGS FOR LONG-TERM USE

1. Orlistat

Orlistat (Xenical[®]) was first approved by the FDA in 1999. Today, it remains the longest licensed anti-obesity drug for long-term use and is available over the counter (Alli[®]). As a non-central nervous system agent, orlistat 120 mg is prescribed for adults and adolescents ≥ 12 years of age [19].

1) Mechanism of action

Unlike other anti-obesity drugs on the market, orlistat does not exert its effect by affecting appetite; instead, it reduces calorie absorption. The main mechanism of orlistat is the inhibition of gastric and pancreatic lipases, which leads to a ~30% decrease in the absorption of intestinal triglycerides and thus calories [20]. Orlistat is expected to have little effect on weight loss with non-fatty food consumption.

2) Side effects

Common side effects of orlistat include fatty/oily stools, increased defecation, fecal urgency, and flatus with discharge. However, by co-prescribing a fiber-containing supplement—psyllium, its gastrointestinal side effects can be reduced.

3) Clinical efficacy

In the XENDOS (XENDOS (XENical in the prevention of Diabetes in Obese Subjects) trial, the largest

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

Drug	Product name	Application	Mechanism of action	Main adverse effect	Contraindication	FDA approval	EMA approval	Korea approval
Orlistat	Xenical [®] , Alli [®]	60 or 120 mg TID during or within 1 hour of a fat-containing meal	Gastrointestinal and pancreatic lipase inhibitor; decrease lipid absorption	Oily stools, oily spotting, fecal urgency, fecal incontinence, hyperdefecation, flatulence with discharge, deficiency in vitamins A, D, E, and K	Pregnancy, cholestasis, malabsorption	Yes 1999	Yes 2012	Yes 2000
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	Yes 2019
Naltrexone/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	Yes 2016
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	Yes 2017
Lorcaserin	Belviq [®] , Belviq XR [®]	10 mg BID 20 mg extended release QD	Serotonin 2C receptor agonist; reduce food intake	Headache, dizziness, fatigue, nausea, constipation, dry mouth	Pregnancy, severe renal disease	Yes 2012	No	Yes 2015
						Withdrawn from the market in February 2020		Withdrawn from the market in February 2020

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

randomized controlled trial (RCT) that evaluated the effect of orlistat in 3,305 patients, orlistat was found to cause a total body weight loss of 2.4% after 4 years. More importantly, it significantly lowered the risk of type 2 diabetes mellitus (T2DM), compared to placebo (6.2% *vs.* 9.0%), over 4 years [21]. Orlistat also improved blood pressure (BP), insulin sensitivity, and lipid profiles owing to its primary action of decreasing intestinal fat absorption. However, in this study, 91% of participants administered orlistat experienced at least one gastrointestinal event and 8% withdrew from the study due to adverse events. Further, there are concerns regarding the potential risk of colorectal cancer due to the presence of excess fat in the colon. In animal models, orlistat was associated with clusters of apoptosis-resistant, neoplastic, premalignant colonic lesions [22]. However, a large retrospective matched cohort study (n=33,625 on orlistat; 160,374 on placebo) showed no evidence of an increased risk of colorectal cancer after the initiation of orlistat [23]. Meanwhile, a significant decrease in the absorption of vitamins A, D, E, and K was observed in participants administered orlistat [21]. To prevent possible deficiencies in fat-soluble vitamins (such as vitamin D), a supplement can be recommended.

2. Lorcaserin

Lorcaserin (Belviq[®] and Belviq XR[®]) is a selective agonist of the 5-hydroxytryptamine (5-HT) 2C receptors and a Drug Enforcement Administration (DEA) schedule IV-controlled medication. In 2016, its extended released (XR) form (once daily [QD] 20 mg of lorcaserin) was approved by the FDA following twice-daily (BID) 10 mg of lorcaserin in 2012. However, on February 13, 2020, the FDA requested that the drug manufacturer voluntarily withdraw lorcaserin from the US market because it was determined that potential risk of cancer associated lorcaserin outweighs the benefits [24]. It was an update to the FDA Drug Safety Communication: Safety clinical trial shows possible increased risk of cancer with weight-loss medicine Belviq, Belviq XR (lorcaserin) issued on January 14, 2020 [25]. This withdrawal came after the FDA's reviewing data from the Cardiovascular and Metabolic Effects of Lorcaserin in Overweight and Obese Patients – Thrombolysis in Myocardial Infarction 61 (CAMELLIA-TIMI 61) clinical trial to evaluate the risk of CVD problems [26]. It was a randomized, double-blind, placebo-controlled, multi-

center, parallel group trial conducted between January 2014 and June 2018 in the US, Canada, Mexico, the Bahamas, Europe, South America, Australia, and New Zealand. The study population consisted of 12,000 men and women who were overweight or obese. Patients were required to have either established CVD, or to be at least 50 years old for men or 55 years for women with T2DM plus at least one additional cardiovascular risk factor. Eligible patients were assigned randomly to either lorcaserin 10 mg BID or placebo. Approximately 96% of patients completed the study, and 62% who completed remained on treatment at the end of study. The median follow-up time was 3 years and 3 months. The primary safety analysis showed no meaningful difference between lorcaserin and placebo in the risk of major adverse cardiovascular events, demonstrating noninferiority. However, it was found that more patients taking lorcaserin (n=462; 7.7%) were diagnosed with cancer compared to those taking a placebo, which is an inactive treatment (n=423; 7.1%). A range of cancer types was reported, with several different types of cancers occurring more frequently in the lorcaserin group, including pancreatic, colorectal, and lung. There was no apparent difference in the incidence of cancer over the initial months of treatment, but the imbalance increased with longer duration on lorcaserin.

On the other hand, lorcaserin has failed to gain approval from the European Medical Agency (EMA) due to preclinical data that revealed the potential of breast cancer development and concerns regarding psychiatric issues—the aggravation of depression, suicidal ideation, and psychosis and valvulopathy. Moreover, phase III studies to determine the difference in adverse event incidence between groups were deemed underpowered [27].

1) Mechanism of action

Lorcaserin decreases food intake by increasing satiety through its serotonin anorectic effect by stimulating the proopiomelanocortin (POMC) receptors in the arcuate nucleus of the hypothalamus [28]. At least 14 serotonin receptor subtypes that modulate different physiological functions, ranging from hallucinations to muscle contraction, exist [29]. The side effects caused by non-specific serotonin agonists (*i.e.*, fenfluramine and dexfenfluramine) are due to the stimulation of the peripheral serotonin 2B receptor. Fenfluramine is a predominant 5-HT_{2b} receptor agonist that is believed to cause adverse CVD effects by stimulating mitotic

activity and subsequent cell overgrowth within the valve leaflets [30]. Owing to its high selectivity for 5-HT_{2c} receptor (15-fold and 100-fold selectivity over the 5-HT_{2A} and 5-HT_{2B} receptors, respectively), lorcaserin can suppress appetite and hunger without triggering pulmonary hypertension or valvular heart defects [31]. Many studies suggest that lorcaserin has multiple psychological effects—reducing craving and impulsivity and elevating satiety), which contribute to weight loss.

2) Side effects

The common side effects of lorcaserin include nausea, headache, dizziness, fatigue, dry mouth, cough, constipation, hypoglycemia, and back pain.

3) Clinical efficacy

Lorcaserin was evaluated in the BLOOM (Behavioral Modification and Lorcaserin for Obesity and Overweight Management) and BLOSSOM (Behavioral Modification and Lorcaserin Second Study for Obesity Management), randomized, double-blind, placebo-controlled phase III trials, which sought to investigate the efficacy and safety of different doses of lorcaserin. In the BLOOM study, 3,182 participants aged 18–65 with a BMI ranging from 30–45 kg/m² received either 10 mg lorcaserin BID or placebo for 52 weeks [32]. At the end of the trial, participants in the lorcaserin group continued the intake of lorcaserin at the same dose or placebo for an additional 52 weeks. All patients were given diet and exercise counseling. At the conclusion of the trial, a weight loss greater than 10% was achieved in 22.6% of participants in the lorcaserin group *vs.* 7.7% in the placebo group. Of the participants administered lorcaserin for an additional 52 weeks, 67.9% of those who had an initial weight reduction >5% maintained this loss compared to the 50.3% patients re-randomized to receive placebo. In the BLOSSOM study, 4,008 patients between 18–65 years of age with a BMI from 30–45 kg/m² received either 10 mg QD or 10 mg BID of lorcaserin or placebo. After 52 weeks, significantly more participants administered either 10 mg QD or 10 mg BID of lorcaserin lost >10% of body weight (22.6% and 17.4%, respectively), compared to 9.7% in the placebo group [33]. In a more recent RCT, 12,000 patients with a BMI >27 kg/m² and confirmed CVD in men >50 or women >55 years of age were administered 10 mg BID lorcaserin *vs.* placebo. This study primarily assessed the cardiovascular safety and efficacy of this medication

after 1 year. Based on the findings, 14.6% of subjects in the lorcaserin group had lost >10% weight compared to 4.8% of subjects in the placebo group who had a similar CVD risk at the 3.3-year median follow-up [34]. Lorcaserin resulted in a weight loss of ~3.3% from the baseline total body weight and improved fasting glucose, fasting insulin, and hemoglobin A1c (HbA1c) levels. In a smaller cohort of the BLOOM-DM (Behavioral Modification and Lorcaserin for Overweight and Obesity Management in Diabetes Mellitus) trial, which comprised 603 overweight or obese patients with T2DM and HbA1c 7.0% to 10.0%, a mean reduction in HbA1c was found in the lorcaserin group compared to the placebo group (0.9% *vs.* 0.4%) [35]. Due to the concerns regarding the potential effect of lorcaserin on other types of 5-HT receptors, which could thus affect valvular competency, patients were monitored with serial echocardiograms during these phase III trials. A pooled risk of 1.15 (95% confidential interval=0.81–1.67) was found for the FDA-defined valvulopathy, suggesting that an unacceptable increase in the risk of valvulopathy was not present with the use of lorcaserin [36]. Although many long-term trials demonstrated beneficial effects of lorcaserin in T2DM and its substantial CVD safety profiles, weight loss efficacy of lorcaserin is only modest.

3. Phentermine/topiramate

Phentermine/topiramate ER (Qysmia[®]) was approved by the FDA in 2012 as the first combination agent for the long-term management of obesity. However, the EMA has not approved this medication due to its abuse potential, the lack of long-term data on the cardiovascular effects of phentermine, and the cognitive side effects of topiramate—attention, language, and memory impairment [27]. As this drug combination contains phentermine, it is a controlled DEA schedule IV substance.

1) Mechanism of action

This drug combination mainly suppresses appetite through mechanisms that remain unclear. The central sympathetic action of phentermine, a noradrenergic agonist, is to enhance the release of norepinephrine, dopamine, and serotonin [37]. Topiramate, a gamma-aminobutyric acid agonist, glutamate antagonist, and carbonic anhydrase inhibitor, was approved for the treatment of epilepsy and prophylaxis of migraines [38]. However, significant weight loss was observed

among epileptic patients treated with topiramate, thereby leading to its evaluation in clinical studies for the treatment of obesity. Although the actions of topiramate on the central nervous system have not been completely understood, rodent studies have suggested that it acts as a neurostabilizer and may boost thermogenesis [39,40].

2) Dose escalation and side effects

Phentermine/topiramate is prescribed for QD use. To prevent insomnia, its known side effect, it is recommended that this medication is taken in the morning. According to the package insert, the dose of phentermine/topiramate should be gradually escalated. After a starting dose of 3.75/23 mg QD is administered for 2 weeks, 7.5/46 mg is administered; this dose was best tolerated by the participants in the study. The dose should be administered for a minimum of 3 months before a further increase to the highest dose of 15/92 mg. Additionally, the dose is only increased if the patient fails to achieve a total body weight loss of 3% after 3 months. If the patient tolerates the medication poorly, a slow titration down or off (ideally over 3–5 days) is warranted to reduce the risk of seizure; this result was found in a study where patients with a history of seizures abruptly discontinued topiramate intake [18]. Common side effects of phentermine/topiramate ER include insomnia, paresthesia, dizziness, dry mouth, dysgeusia, and constipation [38]. A fetal safety issue also exists with this medication: it increases the risk of oral clefts. Thus, advice on contraceptive planning is imperative before this medication is prescribed to women of child-bearing age.

3) Clinical efficacy

Regarding weight loss efficacy, adequate assessments of phentermine/topiramate ER have been conducted *via* long-term studies. EQUIP and CONQUER were each one-year, randomized, double-blind, placebo-controlled studies comprising 1,267 and 2,487 participants, respectively [41,42]. The EQUIP trial included non-diabetic patients with a BMI ≥ 35 kg/m² whereas the CONQUER study included patients with a BMI ranging from 27–45 kg/m² and more than two obesity-related comorbid conditions. The study findings enabled the approval of phentermine/topiramate ER by the FDA. In the EQUIP study, the mean weight loss at 1 year for participants in the phentermine/topiramate ER 15/92

mg group was 10.9%, compared to 1.6% in the placebo group. Similarly, in the CONQUER trial, participants administered the same dose of phentermine/topiramate ER for 1 year achieved a 9.8% reduction in weight from baseline, compared to 1.2% in the placebo group. In the CONQUER trial, patients administered phentermine/topiramate ER 7.5/46 mg for 1 year had a total body weight loss of 7.8%. Notably, both studies demonstrated an improvement in the cardiovascular risk factors. The SEQUEL study, a 2-year extension trial, was performed to assess the sustained weight loss of participants after completion of the CONQUER trial [43]. The study findings reinforced previous findings that phentermine/topiramate ER intake can result in meaningful weight loss and significant improvements in BP, lipid profiles, fasting glucose, fasting insulin, and WC.

4. Naltrexone/bupropion

Naltrexone/bupropion (Contrave[®]) is a drug combination for the long-term management of weight loss. In 2014, this combination was approved the FDA (Mysimba[®] approved by the EMA). Each component of this medication has been used in other medical conditions since the 1980s [18]. As there is no potential of abuse with this medication, it is not a controlled substance.

1) Mechanism of action

As an antidepressant, bupropion is used as a smoking cessation aide. Its anorectic mechanism of action involves the inhibition of dopamine and norepinephrine reuptake. Naltrexone was approved for the treatment of opioid and alcohol addiction and antagonizes an opioid-dependent feedback loop that limits the effects of bupropion on the POMC neurons; hence, this drug combination works synergistically [44].

2) Dose escalation and side effects

A slow dose escalation of naltrexone/bupropion is recommended to minimize the side effect of nausea, with a starting dose of 8/90 mg (a single combination tablet) QD for 1 week (at week 2; 1 tablet BID in the morning and evening, at week 3; 2 tablets in the morning and 1 tablet in the evening, at week two tablets BID (the maximum dose). Typical side effects include headache, dizziness, dry mouth, and gastrointestinal discomfort (*i.e.*, nausea, vomiting, constipation, or diarrhea). Although naltrexone/bupropion results in significant weight reduction and long-term evidence to support its

efficacy exists [18], its side effects of elevation of BP and heart rate make it challenging to prescribe to patients with significant CVD.

3) Clinical efficacy

Naltrexone/bupropion was assessed in four phase III multicenter, long-term, double-blind placebo-controlled trials. The COR (Contrave Obesity Research)-I (n=1,742), COR-II (n=1,496), and COR-BMOD (Behavior MODification) (n=793) trials included patients with a BMI ≥ 27 kg/m², at least one weight-related comorbid condition (i.e., hypertension [HTN]), and COR-DM (Diabetes Mellitus) [45-48]. The percent weight loss observed in COR-I, COR-II, and COR-BMOD in patients administered naltrexone/bupropion 32/360 mg for 56 weeks compared to placebo was 6.1% vs. 1.3%, 6.4% vs. 1.2%, and 9.3% vs. 5.1%, respectively [49]. The final study, the COR-DM trial, evaluated weight loss in 505 patients with T2DM who were either overweight or obese [48]. Here, patients administered naltrexone/bupropion 32/360 mg for 56 weeks vs. placebo lost 5.0% vs. 1.8%. Moreover, their HbA1c was reduced relative to the baseline value (0.6% vs. 0.1%) [50]. These trials revealed improvements in high-density lipoprotein cholesterol and triglycerides in naltrexone/bupropion-treated patients. However, improvements in WC, fasting insulin, and insulin resistance index (homeostasis model assessment of insulin resistance, HOMA-IR) were only identified in participants in the COR-I, COR-II, and COR-BMOD studies [51].

5. Liraglutide

Liraglutide (Saxenda[®]) is an injectable glucagon-like peptide 1 (GLP-1) derivative that was approved by the FDA in 2014 for weight management (dose, 3.0 mg subcutaneous [SC] daily). This approval followed that of a lower dose (1.8 mg daily [Victoza[®]]) in 2010 for T2DM management [52].

1) Mechanism of action

After meals, GLP-1 is secreted from the distal ileum, proximal colon, and the vagal nucleus of the solitary tract and exhibits multiple effects as an incretin hormone [53]. GLP-1 mainly regulates blood glucose by enhancing insulin secretion from the pancreatic beta-cells and inhibits glucagon secretion in a glucose-dependent manner. GLP-1 also induces postprandial satiety and fullness, slows gastric emptying, and decreases appetite

and food consumption by acting on the hypothalamus, limbic/reward system, and cortex [54]. Unlike human GLP-1, liraglutide is more stable in plasma and binds strongly to plasma proteins, thereby enabling a much longer half-life (13 hours) than the human endogenous GLP-1 (a few minutes) [55].

2) Dose escalation and side effects

The optimal dose of liraglutide for weight loss is 3 mg daily; however, to prevent the side effects of nausea and vomiting, treatment should be initiated with 0.6 mg QD and gradually escalated each week by 0.6 mg up to 3 mg [38]. Previously, a meta-analysis revealed that among all FDA-approved anti-obesity medications, liraglutide had the highest discontinuation rate due to its side effects (13% of patients) [56]. The most frequent placebo-subtracted side effects were nausea (25.0%), vomiting (12.2%), diarrhea (11.6%), constipation (11.0%), and dyspepsia (6.4%), which were tolerated by most patients over time [57-59].

3) Clinical efficacy

Liraglutide was approved based on the results of three main RCTs; The SCALE Obesity and Prediabetes, the SCALE Diabetes and the SCALE Maintenance [58,60,61]. In the SCALE Obesity and Prediabetes, obese participants (n=2,487), including 61.2% of the prediabetic cohort, received liraglutide 3 mg QD or placebo. After 56 weeks, a weight loss of 8.0% was achieved in the liraglutide group (vs. 2.6% of placebo) and 63.2% and 33.1% of the participants in the liraglutide group achieved $\geq 5\%$ and $\geq 10\%$ weight reduction, respectively [58] (vs. 27.1% and 10.6% in the placebo group, respectively). Moreover, cardiovascular indicators, including BP and lipid profiles, were better improved in the treatment group. Particularly, HbA1c ($-0.30\% \pm 0.28\%$) and fasting glucose levels (-7.1 ± 0.8 mg/dL) were significantly reduced in subjects administered liraglutide 3.0 mg compared to placebo. The SCALE Diabetes assigned overweight or obese patients with T2DM (n=846) to receive liraglutide 3 mg QD or 1.8 mg QD or placebo for 56 weeks and reported a decrease in the weight of the patients (6.0%, 4.7%, and 2.0%, respectively) [58]. Early achievement of weight loss $\geq 4\%$ with liraglutide 3 mg (at 16 weeks) was associated with greater weight reduction at the study's termination [62]. Compared to the 1.8 mg SC daily group, the liraglutide 3.0 mg SC daily group had a greater improvement in the T2DM

measures, including HbA1c, fasting plasma glucose, HOMA-IR, and number of hypoglycemic agents. The SCALE Maintenance aimed to evaluate weight maintenance in non-diabetic participants who underwent a ≥ 4 -week run-in with a low-calorie diet. Subjects who lost $\geq 5\%$ of their body weight ($n=422$) were randomized to receive liraglutide 3.0 mg SC daily or placebo for 56 weeks. The liraglutide 3.0 mg SC daily group achieved an additional weight loss of 6.2% (0.2%, placebo) [61]. One of the main benefits of liraglutide, besides weight loss, is its favorable effects on CVD outcomes in obese patients with T2DM.

Despite initial considerations of the risk of acute pancreatitis, long-term trials suggest that the risk of this disease does not significantly increase with liraglutide [63,64]. Particularly, biomarkers of acute pancreatitis—amylase and mainly lipase—increase in a non-dose dependent manner during treatment with GLP-1 receptor analogs. However, their increase was not accompanied by symptoms; moreover, when monitored, acute pancreatitis could not be predicted [65]. Based on rodent studies that demonstrated the proliferative effect of liraglutide on thyroid C-cells, contraindications for liraglutide include patients with (or a family history of) medullary thyroid carcinoma or type 2 multiple endocrine neoplasia [27]. In rodents administered incretin-based medications, pancreatic, intestinal, and breast neoplasms were found to develop more frequently; however, these results were not found in human studies [66-68]. A phase IIIb RCT reported no difference in calcitonin levels and medullary thyroid carcinoma rates between liraglutide (≤ 1.8 mg) and placebo during a follow-up of 3.5–5 years [69]. Additionally, the total risk of malignant and benign neoplasms, including pancreatic cancer, was not found to increase in the liraglutide *vs.* placebo group [63,64,70]. However, these results should be interpreted cautiously and an intensive post-marketing surveillance of liraglutide should be performed as the studies were not designed to assess cancer risk and the incidence of medullary thyroid carcinoma was too low for detection in the trials. As no concern regarding neuropsychiatric safety was reported, this medication can serve as a good option for obese patients with mental disorders [71] if they can afford this costly medication (liraglutide 3.0 mg) and agree to a daily injection.

COMBINATION OF ANTI-OBESITY DRUGS IN CLINICAL DEVELOPMENT

As obesity occurs *via* multifactorial pathways, a single drug might exhibit limited efficacy. Thus, a high dose might be required, which often causes unacceptable side effects. Combination therapy comprising multiple anti-obesity drugs with complementary modes of action is warranted to broaden the target energy regulatory systems *via* actions on distinct mechanisms, which could maximize the effect on weight management while maintaining safety and tolerability [72]. To date, however, there has been no approved combination agent for obesity management, besides phentermine/topiramate and naltrexone/bupropion. Other co-administered medications have been investigated to elucidate their long-term efficacy and adverse events [15,16]. Most combinations primarily focus on both controlling hunger/appetite/satiety and inhibiting peripheral calorie absorption (*i.e.*, phentermine/sodium glucose co-transporter 2 [SGLT-2] inhibitor, a GLP-1 agonist/other gut hormones, or an SGLT-2 inhibitor). SGLT-2 inhibitors, such as dapagliflozin, empagliflozin, and canagliflozin, block glucose reabsorption from the renal tubules and result in glycosuria. Therefore, they are primarily used by diabetic patients for blood sugar control [73]. Interestingly, these drugs are effective, to some extent, in individuals without diabetes [74]. Theoretically, the amount of glucose loss in urine is approximately 75 g/d (300 kcal energy deficit). Resultantly, 7–8 kg of weight loss owing to these medications can be expected in patients with diabetes over 6–12 months. However, in previous clinical studies with diabetic patients, only 2–3 kg weight loss was achieved with such agents; this was attributed to compensatory hyperphagia/increased appetite [75]. Thus, combining an appetite suppressor, such as phentermine, with a SGLT-2 inhibitor can serve as a good option for weight management. In a recent clinical trial that examined canagliflozin 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) [76]. Similarly, SGLT-2 inhibitors combined with a GLP-1 agonist caused a greater weight reduction than individual administration of each agent [77].

INITIATING AND TERMINATING PHARMACOTHERAPY FOR OBESITY

Despite the marked availability, anti-obesity drugs are reported to be underused by healthcare providers [3,78]. Only 2% of obese adults who are eligible for obesity pharmacotherapy receive prescriptions for these agents from their doctor [79]. As a highly stigmatized disease, there remains a misconception that obesity is mainly due to a lack of willpower and representative of laziness; thus, these patients are considered undeserving of proper treatment with medications or surgery [80]. The high cost of these medications also prevents adequate prescription for long periods. Weight loss is extremely challenging to achieve and sustain, and long-term management of obesity often requires adjunctive pharmacological interventions. Today, practitioners have access to several FDA-approved options. Moreover, as there is growing evidence that these drugs can delay the onset of obesity-related complications and improve metabolic and cardiovascular parameters, they should be considered in a timely manner.

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. Further, 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 [13,14]. At every visit, physicians should discuss the adverse events that accompany a given drug and evaluate the drug's effect on weight loss. The goal of treatment with anti-obesity drugs in obese individuals should be long-term maintenance of weight reduction and improvement in overall health.

In most clinical trials that evaluated pharmacologic interventions for more than 12 months, a weight loss of 4% to 8% was typical [56]; however, this is rather disappointing considering the high prices of these drugs. Therefore, upon initiation of an anti-obesity medication, health providers must communicate several important messages to their patients. First, not every drug will produce effective results in patients and individual responses will vary widely. Second, when the maximal therapeutic effect of a drug is achieved, a plateau will be reached. Lastly, when drug therapy is discontinued, weight regain is normally expected.

Treatment response to most of these drugs should be evaluated at around 12 weeks using the maintenance dose. A trial period of 3 to 4 months is essential for predicting whether a patient might achieve a clinically significant weight loss at 1 year (classified as responders or non-responders); this is supported by data that early weight loss with any medical intervention is a good indicator of long-term outcomes [62,81-83]. Recently approved anti-obesity drugs have “stopping rules” that are suggested by the FDA and EMA to help clinicians identify patients that might achieve a weight reduction >5% within 1 year. Stopping rules can avoid unnecessary exposure and enhance the risk-benefit ratio [27]. If <5% weight loss is achieved after 12 weeks of treatment with a full dose (<4% weight loss at 16 weeks for liraglutide), the medication should be discontinued and other drugs should be considered. However, it can be difficult for practitioners to determine whether to continue the use of a given anti-obesity drug at the twelfth week, if the full dose has not been administered. Additionally, stopping rules are based on the results of the trials that conducted combined interventions involving an anti-obesity drug and intensive lifestyle modifications not medication only. Thus, the decision regarding the further continuation of a given medication should be made according to its effectiveness at reducing weight when diet, exercise, and behavioral modifications are adopted. Without a low-calorie diet and an increase in physical activity, the application of a medication alone could lead to failure to achieve weight reduction of 5% even after 12 weeks of treatment.

CONCLUSION

As the morbidity and mortality of obesity have significantly increased, most current guidelines recommend pharmacotherapy as the second line of treatment for this disorder following lifestyle modifications. Pharmacological treatment should be considered as part of a comprehensive strategy for the treatment of patients with a BMI ≥ 30 or ≥ 27 kg/m² and an obesity-related comorbidity—HTN, T2DM, dyslipidemia, and sleep apnea. Additionally, the efficacy of medical treatment should be evaluated after the first 3 months of drug use. Substantial research has been dedicated to the development of a newer generation of anti-obesity drugs. In recent years, many novel agents have undergone phase III clinical trials. Compared to placebo, these drugs cause

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

Drug	Study (duration ≥1 year)	Subject (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)	Odds ratio (95% CrI) for achieving ≥5% weight loss	% of patients with ≥5% weight loss at 1 year (drug/placebo)	% of patients with ≥10% weight loss at 1 year (drug/placebo)	Odds ratio (95% CrI) for discontinuation due to adverse event
Orlistat	17 trials	5,572/5,572	Reduced fat intake or 500–800 kcal deficit/non-specific increase or 30 minutes 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	17.9/8.8	1.84 (1.53–2.21)
Phentermine/topiramate	3 trials	1,802/1,735	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	49.7/8.6	2.29 (1.71–3.06)
Naltrexone/bupropion	5 trials	6,963/5,897	500 kcal deficit/non-specific increase or 30 minutes 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	28.3/9.7	2.64 (2.10–3.35)
Liraglutide	4 trials	3,096/1,649	500 kcal deficit/minimum 150 minutes 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	30.4/8.4	2.95 (2.11–4.23)
Lorcaserin ^a	4 trials	9,453/9,440	600 kcal deficit/30 minutes of moderate exercise per day/yes	3.22 (2.46–3.97)	5.1/2.0	3.10 (2.38–4.05)	42.7/19.7	19.0/6.7	1.34 (1.05–1.76)

CI: confidence interval, CrI: credible interval.

^aWithdrawn from the market for safety issue related to an increased cancer incidence in February 2020.

a significant weight reduction, including meaningful improvements in cardiometabolic profiles, while demonstrating good tolerability and safety in patients with obesity. Data from most recent meta-analyses showed that the overall placebo-subtracted weight reduction (%) with the use of anti-obesity drugs for at least 12 months ranges from 2.9% to 6.8%; phentermine/topiramate (3 trials, -6.8%) liraglutide (4 trials, -5.4%), naltrexone/bupropion (5 trials; -4.0%), lorcaserin (4 trials; -3.1%), and orlistat (17 trials, -2.9%) (Table 2) [56,84-88].

Most prior trials conducted on these medications also performed an intensive consultation on diet and exercise in not only the placebo but also the treatment groups. Thus, these medications were proposed for use as pharmacotherapy in conjunction with healthy eating, physical activity, and behavior modification. Further, prior findings demonstrated that anti-obesity drugs cannot be used as a panacea for the treatment of obesity; instead, they should be used to facilitate weight control.

Conflict of Interest

The authors have nothing to disclose.

Author Contribution

Conceptualization: SYL. Investigation: SYL, YJT. Writing – original draft: YJT. Writing – review & editing: SYL, YJT.

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