Review Article

Pharmacologic therapy of obesity: mechanisms of action and cardiometabolic effects

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Abstract: Obesity is a chronic, relapsing, multifactorial disease, which has become a serious threat to public health globally, as the worldwide prevalence of obesity increases exponentially over time. It has been well established that obesity is associated with multiple adverse cardiometabolic effects. Although lifestyle changes are the first line of therapy for obesity, these are often insufficient in attaining weight loss goals. Orlistat, phentermine/topiramate, lorcaserin, naltrexone/bupropion, and liraglutide are agents that have been approved for the treatment of obesity but their effects on cardiometabolic risk factors and outcomes have not been clearly elucidated. Given the detrimental repercussions of obesity on cardiometabolic health, there is a pressing clinical need to fully understand the effects of these agents beyond weight loss alone. Certain previous weight loss drugs have been withdrawn due to safety concerns and this underlines the need for more careful assessment of the effects of the various pharmacologic agents currently used for the treatment of obesity. This review aims to provide an overview of the mechanisms, efficacy, safety and cardiometabolic effects of the currently available pharmacologic agents for weight loss.

Keywords: Obesity; overweight; orlistat; phentermine/topiramate; lorcaserin; naltrexone/bupropion; liraglutide; cardiometabolic effects

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Introduction

According to the Obesity Medicine Association, obesity is "*a chronic*, *relapsing*, *multifactorial*, *neurobehavioral disease*, *wherein an increase in body fat promotes adipose tissue dysfunction and abnormal fat mass physical forces*, *resulting in adverse metabolic*, *biomechanical*, *and psychosocial health consequences*". Obesity has become a serious threat to public health globally, as the worldwide prevalence of obesity increases exponentially over time. In 2016, the World Health Organization reported that more than 1.9 billion adults, 18 years and older, were overweight [body-mass index (BMI) of 25.0–29.9] and of these over 650 million were classified as obese (BMI of 30.0 or more). Percentage-wise, 39% of adults aged 18 years and over were overweight and 13% were obese in 2016. Moreover, 41 million children under the age of 5 and over 340 million children and adolescents aged 5–19 were overweight or obese in 2016 (1). Worldwide, the incidence of obesity almost doubled between 1980 and 2008 and the age-standardized mean global BMI increased by 0.4–0.5 kg/m^2 per decade in both men and women (2). The US accounts for the highest global incidence of overweight and obesity, particularly in men, with a lifetime risk of approximately 50% and 25%,

respectively (3). Future projections suggest that if the current trajectory is not curbed, by 2030 nearly half of all men and women will be obese, and costs associated with overweight and obesity will amount to 16–18% of total health care expenses in the US (4). However, despite these alarming statistics, only one-third of obese patients are given an obesity diagnosis and/or weight-related treatment advice from their physicians (5).

Adverse sequelae of obesity and need for pharmacologic therapy

Obesity and overweight are fundamentally caused by an energy imbalance between calories consumed and calories expended and are affected by an interaction of environmental factors, genetic predisposition, and human behavior (1,6). Overweight and obese patients are at an increased risk of developing cardiovascular diseases (CVD) (mainly heart disease and stroke), type 2 diabetes mellitus (T2DM), hypertension, musculoskeletal disorders (especially osteoarthritis), as well as certain malignancies (including breast, endometrial, ovarian, prostate, liver, gallbladder, colon, and kidney) (1). As a result, overweight and obesity are associated with an increased risk of death (7,8). Actually, in 2010, overweight and obesity were estimated to cause 3.4 million deaths worldwide (9). Even modest weight reductions of 5–10% from baseline may lead to significant improvements in cardiometabolic risk with consequent decreases in obesity-related morbidity and mortality rates (10,11).

Therapeutic lifestyle changes, such as caloric restriction and increased physical activity, are often insufficient in attaining weight loss goals, as many obese patients either fail to lose weight or regain weight that is lost. Thus, the Food and Drug Administration (FDA) has approved certain drugs that may be used in the management of obesity as an adjunct to lifestyle modification. These medications include orlistat, phentermine/topiramate, lorcaserin, naltrexone/bupropion, and liraglutide (12-16). Here, it has to be noted that certain previous weight loss drugs have been withdrawn due to safety concerns (fenfluramine, phenylpropanolamine, amphetamines, and most recently, rimonabant and sibutramine) (17), and this underlines the need for close follow-up of the patients to assess the effects of the various pharmacologic agents currently used for the treatment of obesity.

Currently, most guidelines recommend pharmacotherapy as the second-line treatment for obesity (after lifestyle modification) with bariatric devices and surgery as third- and fourth-line treatments, respectively (18).

According to current guidelines, pharmacological treatment should be considered as part of a comprehensive strategy of disease management for patients with a BMI ≥30 or ≥27 kg/m^2 with an obesity-related co-morbidity, such as T2DM, hypertension, dyslipidemia, and sleep apnea. The efficacy of pharmacotherapy should be evaluated after the first 3 months of therapy (19). It should be stressed here that drugs are not a panacea for the treatment of obesity but only a mean to facilitate weight loss, as healthy dieting and physical activity are a prerequisite for long-term maintenance of weight loss. Anti-obesity drugs should be used only pursuant to their licensed indications and restrictions.

Orlistat

Orlistat is a reversible inhibitor of pancreatic and gastric lipases, which reduces the absorption of fat from the intestine. Administered at the standard dose of 120 mg three times daily before meals, orlistat prevents the absorption of approximately 30% of dietary fat, thereby reducing caloric intake. The most common side effects of orlistat are gastrointestinal (due to the non-absorbed fats in the intestine) and may include steatorrhea, frequent bowel movements, flatus with discharge, and fecal incontinence. Because orlistat inhibits the absorption of lipid-soluble vitamins, vitamin A, D, E and K supplements should be taken when using orlistat (20-22).

The effectiveness of orlistat in promoting weight loss is modest. Pooled data from clinical trials have shown that the use of orlistat in addition to lifestyle modifications, such as diet and exercise, was associated with a weight loss of about 2–3 kg more than placebo (23).

In addition to the reductions in body weight, orlistat appears to be significantly more effective than placebo in favorably affecting several cardiovascular risk factors, including total cholesterol (TC), LDL cholesterol (LDL-C), LDL/HDL ratio, lipoprotein (a), diastolic blood pressure (DBP), and central adiposity (22). In addition, orlistat improves fasting blood glucose and glycemic control and reduces the incidence of T2DM (22,24).

Phentermine/topiramate

Based on the weight loss attained with phentermine and topiramate as individual agents, as well as the notion that

their combination at lower doses might provide additive or synergistic effects with subsequent improved efficacy and safety, a combination of phentermine/topiramate was developed for once-daily oral dosing to enhance weight loss and improve weight-related comorbidities (25). Phentermine is a potent inhibitor of the norepinephrine transporter and acts as an appetite suppressant via activation of the hypothalamic proopiomelanocortin (POMC) arcuate nucleus neurons (26). Topiramate is an antiepileptic drug, which suppresses appetite through modulation of voltage-gated ion channels, increased activity of the γ-aminobutyric acid (GABA)-A receptor-mediated inhibitory currents and/or inhibition of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)/kainite glutamate receptors (25,26).

In a review of 3 Phase III trials (EQUIP, CONQUER, and SEQUEL), 56 weeks of treatment with phentermine/topiramate (PHEN/TPM), as compared with placebo, led to a statistically significant weight loss of 10.6%, 8.4%, and 5.1% with the 15/92, 7.5/46, and 3.75/23 mg doses, respectively (27). Furthermore, the 52-week extension study (SEQUEL) demonstrated that the weight loss was maintained over 2 years with 9.3% and 10.5% weight loss from baseline for the 7.5/46 and 15/92 mg doses of PHEN/TPM, respectively (27). The drug was generally well tolerated with most common side effects being paresthesias, dizziness, dysgeusia, insomnia, constipation, and dry mouth (27).

PHEN/TPM exhibits a favorable cardiovascular profile, as it has been shown to decrease systolic blood pressure (SBP) and DBP, decrease triglyceride (TG) levels, increase HDL cholesterol (HDL-C), and improve glucose homeostasis. Small, mostly transient, increases in heart rate are seen in some PHEN/TPM-treated subjects; however, there are no associated adverse clinical ramifications (28,29). Actually, in a very recent study, the major adverse cardiovascular events rates among current users of PHEN/TPM combination were lower than those among unexposed former users (30). Furthermore, in a study conducted to evaluate the safety and efficacy of PHEN/TPM for the treatment of moderate-to-severe obstructive sleep apnea (OSA) in obese adults, treatment with PHEN/TPM led to significant weight reductions and concomitant improvements in OSA and related parameters, as compared with placebo. More specifically, significant improvements were observed in respiratory disturbance index (RDI), apnea-hypopnea index (AHI), mean overnight oxygen saturation, Pittsburgh Sleep Quality Index (PSQI), and SBP. Of note, there was a significant positive correlation between the reductions in body weight and the improvements in the AHI scores (31).

Lorcaserin

Lorcaserin is a centrally acting anorexic agent, which acts as a selective agonist of the serotonin type 2C receptors (5-HT2CR) on POMC neurons. This drug has been designed to exhibit the beneficial effects of serotonergic drugs on weight loss but without the unwanted side effects mediated by serotonin receptors type 2A and 2B (32,33).

In the Behavioral Modification and Lorcaserin for Overweight and Obesity Management (BLOOM) trial, after 1 year of treatment, the percentage of patients that lost ≥5% of their body weight was significantly higher in the lorcaserin group, as compared with placebo (47.5% *vs.* 20.3%, respectively, corresponding to an average weight loss of 5.8±0.2 *vs.* 2.2±0.1 kg, respectively). Furthermore, during year 2, a significantly higher percentage of patients who continued to receive lorcaserin than of those who received placebo maintained their weight loss (67.9% *vs.* 50.3%, respectively) (34). On the basis of trial data indicating the emergence of pharmacological tolerance in some patients, it is recommended that if a weight loss of at least 5% is not achieved within 12 weeks of treatment with lorcaserin, the drug should be discontinued since it is unlikely that a meaningful weight loss will be achieved with continued treatment (32). In another multicenter, randomized, placebo-controlled, double-blind, parallel arm trial (BLOSSOM trial), patients receiving lorcaserin 10 mg twice or once daily for 1 year lost an average of 5.8% and 4.7% of their body weight, respectively, as compared with 2.8% with placebo (35). Headache, nausea and dizziness were the most common adverse effects reported with lorcaserin. Importantly, there was no evidence for an increase in cardiac valvulopathy in lorcaserin-treated patients compared with those receiving placebo (34,35).

Lorcaserin treatment was associated with significant decreases in waist circumference, BMI, fasting plasma glucose (FPG), insulin, glycated hemoglobin (HbA1c) levels, and insulin resistance during the first year of therapy. However, FPG and insulin levels tended to increase along with body weight during the second year of therapy (34). Similarly, TC, LDL-C, and TG improved during the first year of therapy, but increased during year 2 (34). The levels of apolipoprotein A-I (ApoA-I) were not affected (35). Both SBP and DPB slightly improved with lorcaserin (34). In addition, lorcaserin caused a significant decrease in high-

sensitivity C-reactive protein (hsCRP) and fibrinogen levels (34). In a randomized placebo-controlled clinical trial, which studied the effects of lorcaserin in patients with T2DM (BLOOM-DM trial), lorcaserin, as compared with placebo, significantly decreased waist circumference, hip circumference, HbA1c, FPG, and insulin resistance, although hypoglycemia was somewhat more frequent with lorcaserin. Heart rate was significantly decreased with lorcaserin. Both SBP and DBP decreased with lorcaserin but not significantly differently from placebo (36).

Naltrexone/bupropion

The fixed combination of naltrexone/bupropion (sustained release) has been approved by the FDA, as well as the in the European Union (EU), for the management of obesity. Naltrexone is an opioid antagonist with a high affinity for the μ-opioid receptor and acts as an appetite suppressant by disrupting β-endorphin-mediated autoinhibition of POMC neurons. Bupropion is an atypical antidepressant, which inhibits the reuptake of dopamine and norepinephrine and produces an anorexic effect via stimulation of the activity of POMC cells in the arcuate nucleus of the hypothalamus (37). Thus, by associating an antagonist of the opioid receptors that blocks the autoinhibitory feedback (naltrexone) with an agent that enhances the activity of POMC cells (bupropion), it renders a synergistic drug combination with at least fully additive effects (38).

Treatment with the fixed combination of naltrexone/bupropion (sustained release) has led to placebo-adjusted weight losses at 56 weeks ranging between 2.5% and 5.2% of initial body weight (39). The combination of naltrexone/bupropion is generally well tolerated with an acceptable side effect profile. The most common side effects of naltrexone/bupropion are nausea, constipation, headache, dizziness, insomnia, dry mouth, and diarrhea (40). In contrast with other centrally acting medications, such as phentermine/topiramate and lorcaserin, naltrexone/bupropion has no abuse potential (41).

The effect of naltrexone/bupropion on glucose homeostasis has ranged from neutral to slightly beneficial with corresponding changes in HbA1c from neutral to a decrease of 0.5%. Naltrexone/bupropion, as compared to placebo, has been shown to increase HDL-C by 3–5 mg/dL, decrease LDL-C by 1–4 mg/dL, and decrease TG by 11–15 mg/dL (39). However, on the other hand, naltrexone/bupropion exerts relatively unfavorable effects on blood pressure and heart rate. More specifically, naltrexone/bupropion increases SBP by 1.1–2.6 mmHg and increases heart rate by 0.8–1.1 beats/min. These findings may be attributed to the bupropion-induced inhibition of the reuptake of dopamine and norepinephrine. Thus, naltrexone/bupropion is contraindicated in patients with uncontrolled hypertension (39).

Liraglutide

Liraglutide is a glucagon like peptide-1 (GLP-1) receptor agonist, which was initially approved for the management of T2DM and later on, based on the results of clinical trials demonstrating the ability of GLP-1 analogs to induce weight loss, it was also approved as a weight loss agent. The weight loss with liraglutide appears to be mediated by appetite suppression and delayed gastric emptying (42).

Treatment with liraglutide has led to placebo-adjusted weight losses ranging between 4.0% and 6.1% of initial body weight (39). The most common adverse effects of liraglutide are nausea and vomiting, which usually occur within the first 4 weeks of therapy (42).

Liraglutide exerts favorable effects on glucose homeostasis, although there appears to be a somewhat increased risk for hypoglycemia. Reductions in HbA1c ranging from 0.33–1.85%, depending on the comparator, have been observed with liraglutide in patients with T2DM (39).

In a network meta-analysis, which studied the effects of GLP-1 receptor agonists on the lipid profiles of patients with T2DM, liraglutide, as compared with placebo, caused a slight mean reduction of HDL-C by 0.39 mg/dL. On the other hand, liraglutide caused a mean reduction of LDL-C, TC, and TG by 4.64, 6.19, and 23.03 mg/dL, respectively, as compared with placebo (43).

Liraglutide appears to have a favorable effect on blood pressure. Treatment with liraglutide was associated with a reduction in SPB by 2.6–3.1 mmHg. However, liraglutide increases heart rate by 3–3.5 beats/min (39). Furthermore, in a study of hypertensive patients with T2DM, treatment with liraglutide, as compared with placebo, was associated with a significant decrease of mean 24-hour SBP by 5.73 mmHg and a slight/non-significant reduction of mean 24-hour DBP by 1.42 mmHg. Again, liraglutide caused a significant increase in the mean 24-hour heart rate by 6.16 beats/min. Of note, the beneficial effect of liraglutide on the 24-hour blood pressure was not associated with an increase in urine sodium excretion (44).

The effects of liraglutide on inflammatory markers and obesity-related hormones are variable (39). However,

liraglutide appears to improve markers of oxidative stress (45) and to significantly decrease levels of hsCRP (46,47).

More importantly, liraglutide has been shown to improve cardiovascular outcomes in patients with T2DM. In a large, multicenter, double-blind, placebo-controlled trial, which included 9,340 patients with T2DM and high risk for CVD, addition of liraglutide to standard care significantly decreased the incidence of the primary composite outcome (first occurrence of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke) by 13%, as compared with placebo. Furthermore, liraglutide reduced cardiovascular mortality by 22% and all-cause mortality by 15%, as compared with placebo (48).

Conclusions

Obesity is a chronic, relapsing, multifactorial disease, which has become a serious threat to public health globally, and is associated with a higher incidence of a number of diseases, including CVD, T2DM and cancer. Lifestyle interventions with adjunctive pharmacotherapy approaches are being used to manage obesity and its cardiometabolic sequelae. Although lifestyle modification, aimed at reducing calorie intake and increasing energy expenditure, remains the cornerstone of management of obesity, its effectiveness is frequently limited by significant weight regain in the long-term. Thus, successful management of obesity may require additional measures and adjunctive pharmacotherapy appears to be increasingly effective in this regard. Furthermore, in view of the escalating global epidemic of overweight and obesity, a paradigm shift in our current approach to obesity management may arguably be necessary with greater attention being given to the role of long-term pharmacotherapy to achieve and maintain the recommended weight loss.

As our understanding of energy homeostasis and its complexity has currently significantly improved, new pharmacological approaches have been developed for the management of obesity. However, the long-term effects of these pharmacological agents are not fully known. Actually, certain previous weight loss drugs have been withdrawn due to safety concerns, and this underlines the need for more careful assessment of the effects of the various pharmacologic agents currently used for the treatment of obesity.

Fortunately, as it becomes evident from the preceding discussion of the current clinical evidence in this review, several currently available pharmacotherapies for weight loss are associated with beneficial cardiometabolic effects. Notwithstanding, further research will be required to identify more efficacious drugs with favorable cardiometabolic effects that would provide significant weight loss with an acceptable side effect profile.

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Footnote

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