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Review Article

Recent Advances in Dietary and Drug Treatment of Obesity: Review Paper

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Abstract

Obesity has become a major health problem and a worldwide concern, and its treatment is evolving. Several health risks are associated with obesity, such as hypertension, hyperlipidaemia, type 2 diabetes mellitus (T2DM), stroke, metabolic syndrome, asthma, and cancer. Unhealthy diet and lack of physical activity are major causes of obesity, but genetic or hormonal factors may also contribute. In order to reduce weight gain caused by excessive calorie intake and low physical activity, a number of pharmacological agents have been developed. These agents exert their action by different mechanisms, including inhibition of dietary fat absorption or stimulation of the secretion of satiety hormones. Particular agents such as sibutramine and rimonabant have been evaluated extensively and recommended for obesity treatment in several countries; however, they were ultimately withdrawn worldwide due to disappointing side effects. In contrast, various new drugs showed promising results and were approved by the FDA for the treatment of obesity. This review discusses the old and currently used anti-obesity drugs: liraglutide, semaglutide, tirzepatide, orlistat, as well as the phentermine/topiramate and bupropion/naltrexone combinations. Efficacy, indications, side effects, and contraindications of different classes of anti-obesity drugs will be reviewed comprehensively in this article.

Key words: overweight, obesity, orlistat, liraglutide, semaglutide, tirzepatide, phentermine/topiramate, bupropion/naltrexone

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INTRODUCTION:

Obesity is a common health problem these days. Any patient is said to be obese or overweight when his/her body weight exceeds the normal average. This is measured by the body mass index (BMI). The BMI of any patient is the body weight in kilograms divided by the square of height in meters. If the BMI for a patient is between 25-29.9, the patient is overweight. When the BMI is 30 or over, the patient is said to be obese. Obesity is the most common nutritional disorder in the world. Worldwide obesity has nearly tripled since 1975 [1]. In 2016, 1.9 billion adults were overweight, and over 650 million of them were obese. In 2020, 39 million children were overweight or obese according to the WHO reports. In 2022, 12.5% of people around the world were obese. In 2024, 39 million children under 5 years old were overweight [2]. In Libya, 25.85% of male adults were overweight or obese, whereas 41.08% female adults were [2]. Children in Libya are also suffering from this disorder (15.4% males vs 13.3% females) [2]. According to the American Heart Association, obesity is one of the major risk factors for cardiovascular diseases [3]. There are many causes of obesity, and to treat any case of it, the cause should be determined. Sometimes, the situation could be caused by more than one cause. Novel drugs have been discovered to treat some cases of obesity, although the cause has not been detected. The well-known causes of obesity are: increase in intake amount more than needed, poor diet (Bad fat and junk food loaded with simple carbohydrates), lack of physical activities, environmental factors (lack of spaces for recreation and exercise), and diseases such as Cushing's syndrome, hypothyroidism, genetic factors and several medicines (corticosteroids, antidepressants, anticonvulsants and smoke cessation). This article will discuss a number of old approved drugs and newly discovered agents that can help in the treatment of obesity, as well as a number of good steps that can help in preventing and protecting people, especially those with medical conditions such as type II diabetes and certain cardiovascular diseases, from obesity.

2.1 Non-pharmacological steps (Diet & Physical Activity)

The effective way of treating obesity is the combination of a low-calorie diet (especially the low – low-carbohydrate and the low–fat) with regular exercise and behavior therapy. By decreasing the daily intake of calories, most overweight and obese patients can decrease their body weight by 0.5 kg in one week [4]. Many studies have been carried out to compare the low-carbohydrate and low–fat diets, suggesting that a low-carbohydrate diet is more effective in losing kilograms from the body and decreasing the risk of cardiovascular diseases by its positive impacts on the lipid profile [5]. Furthermore, drinking water regularly can help in decreasing body weight as well as controlling the body from regaining weight again [6]. Low-calorie versions of healthy diets like Mediterranean or Dietary Approaches to Stop Hypertension (DASH) are other diets involved in obesity management. The Mediterranean diet appears to be important in reducing cardiovascular as well as diabetes mellitus complications [6]. The DASH diet is characterized by few servings of fruit, vegetables, low-fat dairy products & less than 20% of daily calories come from fat. Combining a restricted DASH diet with a daily physical activity has been shown a decrease in weight over 26 weeks [7]. A high-protein diet is another diet that has at least 20% of daily calories come from different sources of protein. The idea of this type of diet is to increase the feeling of fullness & satisfaction after eating. High protein diets as well as low glycemic diets may play a role in weight loss maintenance [7]. Intermittent fasting is also an important method to decrease obesity. Some people fast as a way to decrease weight & others for religious reasons. Cutting off food for many hours or many days per week helps lose weight, but the cons of that are when you stop fasting, the body gains the weight again, so it is just useful for some cases or as a start to lose weight. To promote a typical body weight after weight reduction, regular exercise, besides drinking water, is a recommended step. Reasonable exercise goals are important to get the benefits of physical activities, especially for those who have lived a sedentary life for more than 10 years, because setting a goal of running 3 miles every day is something very difficult, and failure in achieving that goal can lead to depression and more weight gain [8]. Instead of that, the patient can start with very easy and painless exercises and then increase the level gradually. 30 to 60 minutes of exercise per day seems to be an adequate period for preventing weight gain and enhancing weight loss [8]. Behavioral interventions are also important to follow up on the case. Some of these psychological therapeutics' strategies are self–monitoring, goal setting, stimulus control, and social support [6]. Self–monitoring is a step used for decreasing body weight by writing down in a diary everything consumed, whether food or drink, every single day. This can help in two ways: firstly, by improving unhealthy eating behavior for a minute by assessing the nutritional

value, and by providing a good report for exactly what the patient consumed that day to avoid more harmful and unhealthy diets. Self–monitoring technique can be enhanced by social support from a person, a group, or a physician [6].

2.2 Pharmacological therapy

Several drugs are used in cases where the BMI is ≥30 or ≥27 with two or more risk factors or diseases (e.g., T2DM, HTN, dyslipidemia) [9]. Many drugs are approved for obesity treatment, especially for those who may not qualify for surgery [8]. Some (many) drugs are approved for short-term pharmacotherapy & others are approved by the FDA for chronic use [8]. Few drugs are no longer used. However, novel drugs have been approved to treat obesity as well as other diseases (e.g., Semaglutide "Wegovy & Ozempic' & Tirezepatide " Zepbound" in T2DM &) [8]. Table 1 shows the approved drugs by the FDA for long-term use.

2.2.1 Sibutramine is one of the drugs that have been evaluated extensively in several research & recommended for short-term use (<12 weeks); however, it is not approved by FDA. It is a serotonin–norepinephrine reuptake inhibitor that reduces appetite. Using both the Sibutramine and the non-pharmacological steps was more effective than using the drug or the steps alone [9]. Due to its adrenergic effects, mild increases in blood pressure and heart rate are the main side effects, and therefore, the blood pressure should be monitored regularly, especially in those who are more susceptible to the disease [9, 10]. This drug was withdrawn in 2010 as a result of the increased risk of heart attack & stroke in high-risk cardiac patients.

2.2.2 Rimonabant is a cannabinoid receptor CB1 antagonist which has not been approved by the FDA because of its undesirable adverse effects of depression, anxiety, nausea, and diarrhea. It was approved in 2006 for the treatment of obese patients by most European countries, Mexico, and Argentina [6],but it was withdrawn worldwide in 2008 due to its serious psychiatric side effects [10, 11].

2.2.3 Orlistat (Xenical) is another anorexic drug that works by inhibiting the triacylglycerol lipase enzyme (Lipase Inhibitor) in the intestinal lumen, which is responsible for reducing fat absorption up to 30% [12]. It is approved for long-term use; however, it should be discontinued if the patient cannot lose 5-7% of his/her weight within 12 weeks. This drug is more powerful in the presence of dietary fat, but it may increase the rate of side effects. It is important to advise patients to decrease fat amount in meals to reduce the severity & frequency of adverse effects [12]. The main adverse effects of the drug are greasy spotting, flatus with discharge, increased defecation, and fecal urgency; however, they are short- time existing. Orlistat can also interfere with the absorption of lipid-soluble vitamins (A, D, E, K); thus, vitamin supplements are recommended [13]. A trial has been conducted that shows that using Orlistat for 4 years can decrease the risk of diabetes [13]. The combination of both Sibutramine and Orlistat has no benefit over using each drug alone. Orlistat is contraindicated in pregnancy, in patients with chronic malabsorption syndrome, and in patients with a history of oxalate-induced renal stones [14].

2.2.4 Phentermine (Adipex) and diethylpropion are sympathomimetic drugs that stimulate adrenergic receptors and enhance norepinephrine production in certain brain regions that are responsible for reducing food intake. As with Sibutramine, Patients who receive these drugs should be closely monitored for blood pressure. Other side effects are dry mouth, dizziness, and insomnia (should not be taken late at night). They are contraindicated in CHF, stroke, glaucoma, hyperthyroidism & heart diseases [15]. Low rate of addiction to these drugs is reported by the "Drug Enforcement Agency," and they are therefore approved for only a few weeks [15].

2.2.5 Phentermine and topiramate (Qsymia): is a combined form of two drugs that is approved by FDA for long-term use. Topiramate is an anti-epileptic drug decreases appetite & increases satiety by activating gamma-aminobutyric acid receptors [16]. This combination drug was approved by FDA in 2012. Weight loss is more with the combination form in comparison to the mono-therapy components. Starting with a low dose 3.75/23 mg for 12 weeks, and after that if a 3% loss in weight is not achieved, the dose can be increased to 11.25/69 mg for 14 days and then to high dose (15/92 mg) daily to achieve 5% decrease in body weight after 12 weeks [17]. The drug should be discontinued gradually by tapering the dose if the score is not achieved [17]. Side effects include dizziness, drowsiness, dry mouth, constipation, difficulty sleeping & metallic taste. Other serious side effects are depression & suicidal thoughts or actions. Serious Eye problems with pain & redness that may lead to permanent vision loss if untreated [17]. This drug combination is contraindicated during

pregnancy, in uncontrolled hypertension, hyperthyroidism, and glaucoma [17].

2.2.6 Leptin Analogs Leptin is a hormone derived from the fat cell and responsible for telling the brain how much fat is stored in the body [18]. Leptin is known for the energy balance & hunger control [18]. Its MOA is binding to leptin receptors (ObRs), which are found in both brain & peripheral tissue, activating the Janus kinase-signal transducer (JAK2-STAT3), which is important in homeostasis, as well as activating phosphatidylinositol 3-kinase, which regulates food intake & glucose metabolism [19]. Recombinant methionyl human leptin **(Metreleptin)** was given to nine female patients with lipodystrophy and a serum leptin level of less than 4 mg/ml. Eight of those ladies were diabetics. During the treatment, the lipid profile was recorded, and the level of triglyceride decreased by 60%. The glycosylated hemoglobin level also decreased by 1.9%. The levels of T3, T4, and leptin were decreased when the body weight decreased by 10%. This may explain the changes in body weight and the endocrine system as a result of leptin disturbance and the ability to overcome the problem by replacement leptin therapy [19]. Metreleptin was approved by FDA in 2014 as an adjunct to diet to treat patients with congenital or acquired generalized lipodystrophy [20] & therefore it is contraindicated in general Obesity with no leptin deficiency to avoid leptin resistance [21].

2.2.7 Bupropion/Naltrexone (Contrave) BN: Bupropion is a dopamine reuptake inhibitor that increases dopamine activity in the brain. **Naltrexone** is an opioid strong mu receptor antagonist that blocks the receptors on the POMC, preventing negative feedback of these cells, which in turn increases POMC activity. BN may reduce appetite as well as increase energy expenditure by activating pro-opiomelanocortin (POMC) cells. It may also regulate the dopamine reward system that helps in controlling pleasurable stimuli (food, sex & drugs of abuse) & overeating behaviors [22,23]. A comparison between different doses of BN to mono-therapy or placebo showed that BN decreased weight more than mono-therapy or Placebo alone [24]. NB showed an important reduction in visceral & total body fat [25]. However, this drug combination may induce several adverse effects such as nausea, vomiting, headache, constipation, dry mouth, and insomnia. Bupropion/Naltrexone should not be prescribed for those people who have seizure disorders, bulimia nervosa, or a history of alcohol withdrawal seizures. It is also contraindicated in pregnancy, uncontrolled hypertension, chronic opioid use, severe renal or hepatic disorder [25].

2.2.8 Glucagonlike Peptide-1 Agonists (GLP-1) GLP-1 are an Incretin analogue released after meal & stimulate insulin secretion with glucagon inhibition. They promote weight loss in patients with or without T2DM [26]. Some have been approved lately by the FDA to be used in long-term treatment of obesity & others are still under clinical phases.

2.2.8.1 Liraglutide is one of the GLP-1 that was approved by the FDA for long-term use. It is given subcutaneously & found to decrease many metabolic parameters like the waist circumference, both systolic & diastolic blood pressure & improve dyslipidemia in comparison to placebo [27]. Liraglutide was associated with better quality of life [28]. The main side effects observed were gastrointestinal upsets, cholelithiasis, cholecystitis, and pancreatitis. Liraglutide was tested for diabetic patients in relation to cardiovascular outcomes & mortality compared with placebo, and found a significant reduction in the primary CV outcome as well as CV mortality rate [28]. Liraglutide should not be used in patients with a history of pancreatitis or thyroid cancer or any related diseases of these organs [29].

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

Drugs	Product name	Mechanism of action	Main side effects	Contraindications
Orlistat	Xenical	GI and pancreatic lipase inhibitor; reduce lipid absorption	Oily stools Oily spotting Faecal urgency Faecal incontinence Hyper defecation Flatus with discharge	Pregnancy Cholestasis Malabsorption

			Deficiency in vitamins A, D, E and K	
Phentermine/topiramate	Qsymia	NE agonist, GABA agonist, glutamate antagonist; supress appetite	Paraesthesia, dry mouth, constipation, insomnia, anxiety, depression	Pregnancy, uncontrolled HTN, CVD, CKD, glaucoma, hyperthyroidism, patients on MAOIs
Naltrexone/bupropion	contrave	Opioid receptor antagonist/dopamine agonist and NE reuptake inhibitor; reduce appetite, prolong feeling of satiety	Nausea, headache, constipation, dizziness, vomiting, dry mouth	Pregnancy, uncontrolled HTN, seizure, anorexia or bulimia nervosa
Liraglutide	Saxenda	Glucagon-like peptide-1 agonist; Slow gastric emptying, increase satiety, decease food reward	Nausea, diarrhoea, constipation, vomiting, dyspepsia	Pregnancy, personal or family history of medullary thyroid carcinoma or type 2 MEN
Semaglutide	Ozempic/ Wegovey	Glucagon-like peptide-1 agonist; decease hunger, increase feeling of satiety and fullness	Nausea, vomiting, diarrhoea, constipation, abdominal pain, fatigue, headache	Pregnancy, personal or family history of medullary thyroid carcinoma or type 2 MEN, Pancreatitis, sever renal impairment
Tirzepatide	Mounjaro	Dual incretin receptor (GLP-1 & GIP) agonist); slow gastric emptying, reduce appetite, prolong satiety	Nausea, vomiting, dyspepsia, diarrhoea, constipation, abdominal pain, fatigue	Pregnancy, personal or family history of medullary thyroid carcinoma or type 2 MEN, Pancreatitis, sever renal impairment, sever gastrointestinal disease such as gastroparesis

2.2.8.2 Semaglutide is another GLP-1 agonist used in chronic weight management along with diet & exercise in patients with a BMI of ≥30 or ≥27 who have at least one metabolic disorder (HTN, T2DM, or cholesterol disturbance). It is given subcutaneously once per week & it can be indicated for children aged 12 years or older. Like liraglutide, it works by imitating Incretin, a GI hormone that stimulates insulin secretion, inhibits glucagon release, delays gastric emptying, curbs appetite & decreases food absorption [30]. Semaglutide was approved by the FDA in 2021, under the brand name Wegovy. A phase 2 clinical trial was conducted to compare semaglutide versus liraglutide, which showed that semaglutide strongly decreases mean body weight in comparison to liraglutide; however, both effectively reduced weight [31]. Gastrointestinal side effects such as nausea, vomiting, diarrhea, or constipation are relatively common but improve with time. Pancreatitis, gall bladder disorders, and bowel obstruction were also reported in those people who have semaglutide [31]. Both semaglutide & Liraglutide are CI in pregnancy. Semaglutide is also CI in patients with a history of thyroid & pancreatic disorders [30].

2.2.9 Tirzepatide: is a new GLP-1/GIP receptors agonist approved recently (Nov. 2023) by the FDA for chronic weight management in adults with BMI of ≥30 (obese) or ≥27 (overweight) with at least one weight - related condition (HTN, T2DM or dyslipidemia) along with healthy diet & exercise to help in blood glucose improvement as well as decrease weight [32]. Zepbound (trade name) is

administered subcutaneously once weekly, and the dose must be increased gradually to reach the maximum dose of 15mg per week [32]. Zepbound effectiveness was established in 2 randomized, double-blind, placebo-controlled trials of adults with obesity & without diabetes mellitus [33]. The main adverse effects of tirzepatide observed in the SURMOUNT-1 trial include: GIT upsets (nausea, vomiting, diarrhea & constipation), alopecia, Eructation, injection site reaction & hypoglycemia [34]. Tirzepatide contraindications include pregnancy, personal or family history of medullary thyroid carcinoma or type 2 multiple endocrine neoplasia, Pancreatitis, severe renal impairment, severe gastrointestinal disease such as gastroparesis [34]. A study compared tirzepatide to dulaglutide in Japanese patients, showing a superiority of tirzepatide in glycemic control & body weight over dulaglutide [35]. Tirzepatide was also founded to treat cardiometabolic disorders like non- alcoholic fatty liver disease.In conclusion, it seems clear that a new era of obesity treatment has begun by using novel anti-obesity agents with different mechanisms of action. However, incomplete and uncertain data about the effect, safety, and cost-effectiveness of these agents appear as a major concern for their appropriate use. Obesity pharmacotherapy is a rapidly developing field, and further studies on long-term clinical response, safety profile, and cost effectiveness will provide a better understanding of its place in the treatment algorithms for obesity and obesity-related complications over the next years.

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