

Shedding light on weight loss: A narrative review of medications for treating obesity

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List of abbreviation

1. GLP-1: Glucagon like peptide-1
2. CVD: cardiovascular diseases
3. WHO: World Health Organisation
4. BMI: Body Mass Index
5. NIH: National Institute of Health
6. FDA: Food and Drug Administration
7. NO: Nitric Oxide
8. TNF- α : Tumor Necrosis Factor-Alpha
9. IL-6: Interleukin-6
10. PAI-1: Plasminogen Activator Inhibitor-1
11. CRP: C-Reactive Protein
12. EAT: Epicardial Adipose Tissue
13. WC: Waist Circumference
14. VAT: Visceral Adipose Tissue
15. GABA: Gamma-Aminobutyric Acid
16. POMC: Proopiomelanocortin
17. 5HT-2C: 5-Hydroxytryptamine 2C
18. MEN 2: Multiple Endocrine Neoplasias Two
19. GIP: Glucose-Dependent Insulinotropic Polypeptide

Abstract. Obesity and overweight are the major risk factors for numerous chronic diseases, including cardiovascular diseases such as heart disease and stroke, which are the leading causes of death worldwide. The prevalence of obesity has dramatically risen in both developed and developing countries, making it a significant public health concern and a global crisis. Despite lifestyle modifications being the first-line treatment, the high risk of relapse has led to a growing interest in non-invasive pharmacotherapeutic interventions to achieve and maintain weight loss and reverse the growth of the obesity epidemic. Cardiovascular diseases and cancer account for the highest mortality rates among other comorbidities associated with obesity and overweight. Excess and abnormally deposited adipose tissue secretes various inflammatory mediators, leading to cardiovascular diseases and cancers. Weight loss of 5–10% significantly reduces cardiometabolic risk. Medications currently approved in the USA for long-term management of obesity are orlistat, naltrexone, bupropion, phentermine/topiramate, and Glucagon Like Peptide-1 (GLP-1) agonists such as liraglutide and semaglutide. The benefit-to-risk of medications, comorbidities, and individual responses should guide the treatment decisions. The article provides a comprehensive overview and discussion of several weight loss medications used previously and currently, including their efficacy, mechanisms of action, and side effects.

Key words: Cardiovascular diseases, obesity, weight loss medications, cancer, atherosclerosis.

INTRODUCTION

Obesity has become a global health challenge, increasing mortality and healthcare costs and reducing the quality of life by significantly increasing the risk for non-communicable severe diseases, including cardiovascular diseases (CVD), type II diabetes, cerebral vasculopathy, hypertension, arthropathy, gallbladder lithiasis, sleep apnea syndrome, and certain neoplasms such as endometrial or breast cancer [1–3]. According to the World Health Organization [WHO], obesity and overweight are excessive or abnormal body fat accumulation that negatively affects health [4]. Body Mass Index [BMI] is often used as a screening tool for overweight and obesity; a BMI of 25–29.9 kg/m² is considered overweight, while a BMI of 30 kg/m² or higher is considered obesity [5]. Children and adolescents with a BMI between the 85th and 95th percentile for their age and gender are considered overweight, and those with a BMI >95th and >99th percentile are considered obese and severely obese, respectively [6]. The prevalence of obesity has increased substantially worldwide, with a three-fold increase since 1970, with about 13% of adults being obese and about 39% of adults being overweight, and with an estimate that at least one in five people will be obese by 2025 [5, 7, 8]. Obesity rates vary significantly by country, ethnicity, age, and sex. Women tend to have a higher average BMI than men, influenced by cultural norms and gender roles, and diet and physical activity differences [2]. Also, obesity rates tend to increase with age, with the highest rates among adults aged 44–59 [44.3%]. Non-Hispanic black adults have the highest prevalence [49.9%], followed by Hispanics [45.6%], non-Hispanic whites [41.4%], and non-Hispanic Asians [16.1%] [6]. Obesity ranked sixth in global disease burden and second in preventable causes of death after smoking [9, 10]. Healthcare expenses exceeded \$ 700 billion globally and \$100 billion in the USA annually and were extrapolated to cost \$ 432 trillion by 2035 globally [9, 11]. Given the rising disease burden and healthcare expenses, it is crucial to identify and implement a multi-interventional approach to address this health issue [12]. A 5–10% weight loss can significantly improve health and quality of life by decreasing associated comorbidities [9, 13]. Lifestyle and behavioral modifications are the initial keystone interventions for obesity management. Still, pharmacological therapy should be considered for those who have not achieved or sustained weight

loss through lifestyle changes. The U.S. National Institute of Health [NIH] recommends medications for individuals with a BMI > 30 kg/m² or a BMI > 27 kg/m² with weight-related comorbidities [14]. Currently, the Food and Drug Administration [FDA] has approved the following anti-obesity drugs: orlistat, naltrexone, bupropion, phentermine/topiramate, and GLP-1 agonists such as liraglutide and semaglutide [15]. In this review, we discuss obesity pathophysiology and weight-loss medications.

PATHOPHYSIOLOGY

Obesity is a global epidemic influencing almost all organ systems and contributes to the etiology of metabolic diseases such as cardiometabolic syndrome and insulin resistance. Obesity emerged from a complex interaction between genetic and environmental determinants, causing disrupted cellular metabolism, homeostasis, and apoptosis [16]. Obesity is one of the major risk factors associated with CVDs due to its effects on impaired endothelial function caused by reduced nitric oxide (NO), which is linked to an increase in oxidative stress [17–18] or proinflammatory cytokines. Reduced NO function may increase vasoconstriction and vascular resistance, potentially predisposing individuals to hypertension and other CVD risk factors (Fig. 1) [19]. Adipose tissue is a major producer of various substances, including tumor necrosis factor- α (TNF- α), interleukin-6 (IL-6), plasminogen activator inhibitor-1 (PAI-1) linked to BMI with other factors like C-reactive protein (CRP), fibrinogen. They should be considered in clinical settings (Fig. 1) [20–21]. Around 30% of circulating IL-6 may originate from adipose tissue, influencing the production of CRP in the liver. Elevated CRP levels are a marker of chronic inflammation, which can contribute to the onset of acute coronary syndrome [20, 22–23]. Systemic and vascular inflammation caused by visceral fat contributes to every stage of atherosclerosis, including fatty streak development to atherothrombosis [24–25]. Pericardial and epicardial adipose tissues are ectopic fat deposits that play a significant role in the pathogenesis of cardiovascular diseases (Fig. 1) [26]. Pericardial fat is located within the pericardial sac and has been linked to higher BMI, traditional cardiovascular risk factors, and more atherogenic lipoprotein particles [27]. Epicardial adipose tissue (EAT) stems from embryonic brown adipose tissue located between the outer myocardial wall and the visceral pericardium, and the thickness of EAT is linked to waist circumference (WC),

blood pressure, markers of insulin resistance, and dyslipidemia. This depot is highly insulin resistant and may indicate cardiovascular risk due to releasing chemokines and cytokines into the vasculature [27]. Abdominal visceral adipose tissue (VAT) is a predominant visceral fat deposit in the human body, over tenfold larger than pericardial fat [28]. VAT is speculated to have a systemic effect on atherosclerosis due to its significant association with CVD risk factors, metabolic syndrome, and systemic markers of inflammation [29–31]. Although pericardial fat is smaller than VAT, its location around the coronary arteries and myocardium may thus have a paracrine effect on the development of coronary artery disease [28]. Incorporating therapeutic lifestyle changes, such as decreasing calorie intake and increasing physical activity, may not be sufficient to achieve weight loss goals, as many people who are obese struggle to lose weight or regain the weight they have lost. Thus, the FDA has approved certain medications

that can be integrated with lifestyle modifications to manage obesity [34]. Presently approved, all anti-obesity medication assists individuals in restricting their caloric consumption and improving adherence to their dietary regimen, except for Orlistat. The reduction in energy intake primarily occurs by enhancing satiety and reducing appetite and cravings for food [35]. Pharmacotherapies aim to modify the interplay of hormones, receptors, and cells that coordinate to shape our body and its response to environmental factors. Medications that work centrally by directly influencing neurotransmission to target the circuits involved in feeding could potentially impact various physiological functions, notably leading to psychological outcomes like mood disorders [36]. Most guidelines propose pharmacotherapy as the second-line treatment for obesity (after lifestyle modification), with bariatric devices and surgery as third- and fourth-line treatments, respectively [37].

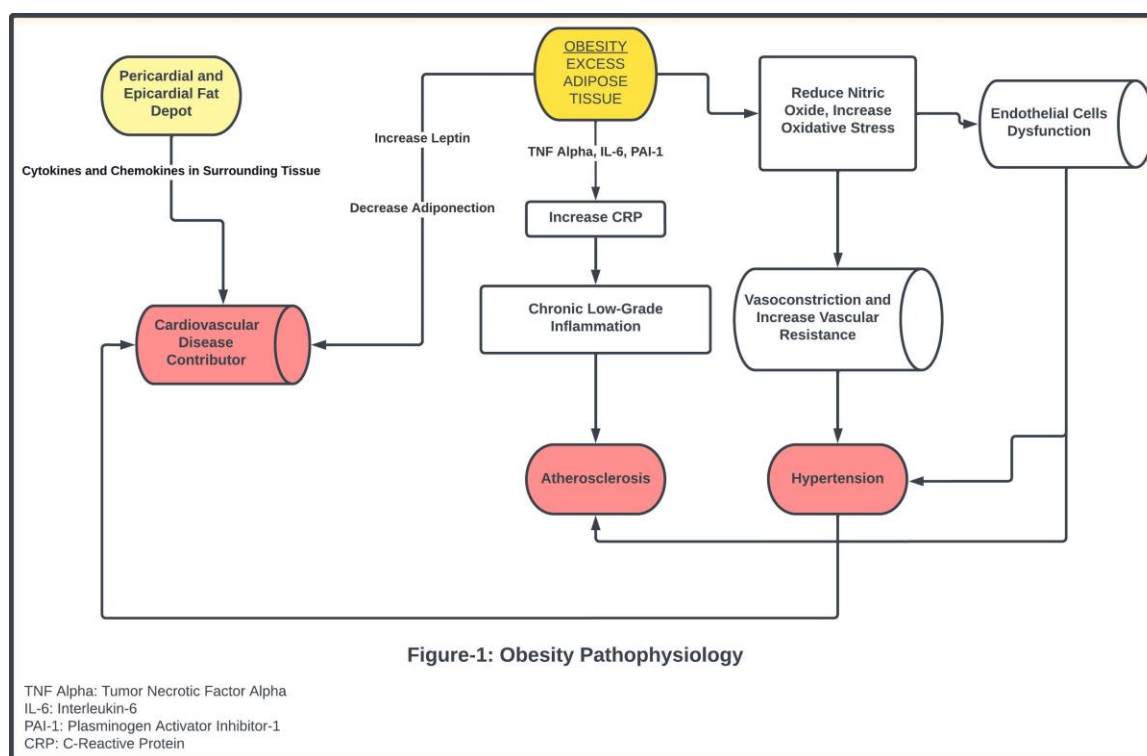


Figure 1. Obesity Pathophysiology.

DISCUSSION

Obesity is a significant risk factor for CVD. Making therapeutic lifestyle adjustments like calorie restriction and increased physical activity, which is frequently insufficient in achieving weight loss goals, makes using medications to reduce weight and

body-to-waist ratio an essential consideration before we can perform bariatric surgeries on these patients. Medication to assist patients in losing weight and maintaining weight loss could improve several areas because obesity is a factor in many ailments, including dyslipidemia, hypertension, and diabetes [38].

DRUGS

Amphetamine derivatives like desoxyephedrine, phentermine, and diethylpropion were among the first drugs used in the 1950s. The 1970s largely discontinued them due to their cardiovascular risk and abuse potential side effects [39]. Phentermine and topiramate combination was approved by FDA in 2012 for the long-term treatment of obesity. Phentermine causes an increase in catecholamines and serotonin activity, leading to direct effects in the hypothalamus and causing anorexic effects [40–41]. Although the exact mechanism of action of the combination, specifically topiramate for weight reduction, is unknown, it is believed that the desired effect occurs due to the involvement of norepinephrine and Gamma-Aminobutyric acid (GABA) agonism and glutamate antagonist leading to appetite suppressing effect [42–43]. An increased dose trial is given with an initial dose of immediate-release phentermine/extended-release topiramate at 11.25mg/69 mg daily for two weeks followed by a final titration to a dose of 15mg/92 mg daily for 12 weeks [43]. In comparison to placebo, phentermine/topiramate medication led to an average weight loss of 7.73 kg (95% CI: 6.60–8.85). The dosage of phentermine/topiramate was responsible for the weight reduction. The weight reduction averaged 3.55 kg (95% CI: 2.22–4.88) for 3.75/23 mg, 7.27 kg (95% CI: 6.40–8.13) for 7.5/46 mg, and 8.25 kg (95% CI: 6.92–9.79) for 15/92 mg when compared to placebo [45]. Patients on anti-diabetic drugs should have their glucose levels checked because weight loss can result in hypoglycemia. Oral contraceptive users should be informed that taking phentermine-topiramate may reduce effectiveness [44].

Orlistat (Brand name Xenical) works by inhibiting gastric and pancreatic lipase in a reversible manner, and at the recommended therapeutic dose of 120 mg three times daily, it reduces fat absorption by ~30% (Table 1) [38]. It showed larger improvements in blood pressure, waist size, total cholesterol, and LDL cholesterol and was associated with a 50% risk reduction in progression to type 2 diabetes mellitus in those with impaired baseline glucose tolerance [46]. The most frequent adverse effects are gastrointestinal, including greasy stools, fecal urgency, discharge-producing flatulence, stool incontinence, and decreased fat-soluble vitamin absorption, which can be improved with regular

vitamin supplementation (Table 1) [38, 41]. During the XENDOS trial, after 4 years, the average weight loss with orlistat was higher (5.8 kg vs. 3.0 kg with placebo; $P < 0.001$) [46].

Bupropion and Naltrexone are a combination of antidepressant medication (norepinephrine and dopamine reuptake inhibitor) and opioid antagonists approved by the FDA for weight loss in the United States in 2014. The hypothesized mechanism for weight loss is primarily through food intake and satiety feedback inhibition. Bupropion, through activation of proopiomelanocortin (POMC), has an appetite-suppressing effect in the hypothalamus. Naltrexone leads to the inhibition of cannabinoid receptors which has appetite-enhancing effects and thus counteracts the increased levels of POMC. Together they act synergistically to stimulate central melanocortin pathways and block inhibitory feedback loops that prevent weight loss in a way that increases energy expenditure and decreases hunger [15][42]. The desired therapeutic dose of bupropion-naltrexone is 16–180 mg twice daily. It is achieved in four doses escalation every week over one month, starting from the initial dose of 8–90 mg daily in the morning. Common side effects include nausea, constipation, headache, vomiting, dizziness, increased blood pressure, increased heart rate, and diarrhea. Bupropion has a black box warning for suicidal ideation and decreasing seizure threshold, so patients should be monitored for mood changes. The combination is contraindicated in patients with eating disorders (anorexia nervosa or bulimia) or previous seizure history, drug addiction history, high risk for angle-closure glaucoma, and uncontrolled hypertension [41]. After one year of therapy, the appetite-suppressing effect of bupropion-naltrexone decreases [44]. And in four studies COR-1, COR-II, COR-BMOD, COR-DM, the participants who took the medicine lost an average of 11 to 22 pounds [47].

Liraglutide (Saxenda) is a GLP-1 analog used in treating type 2 diabetes mellitus and was approved by FDA for weight loss treatment in 2014 as Saxenda. It acts on the hypothalamus and hindbrain and works in three ways to achieve the desired weight loss: improving insulin production, optimizing glucagon secretion based on blood glucose levels, enhancing satiety by delaying stomach emptying, and reducing appetite by influencing the brain regions that control food intake [43]. Initial treatment dosing starts at 0.6 mg with weekly increments of 0.6 mg to a maximum daily dose

of 3 mg. Common side effects include nausea, hypoglycemia, diarrhea, constipation, vomiting, headache, dyspepsia, fatigue, dizziness, abdominal pain, and increased amylase and lipase. Liraglutide is contraindicated in pregnant patients with a previous history of pancreatitis or with a personal or family history of medullary thyroid carcinoma or MEN 2 syndrome (multiple endocrine neoplasia two syndromes) [43].

Semaglutide, like Liraglutide, is a GLP-1 analog approved for the treatment of type 2 diabetes and recently got approved for the management of obesity in 2021 under the brand name Wegovy. The mechanism of action for weight loss is similar to Liraglutide with the same black box warning. The major difference is that Semaglutide has superior weight loss efficacy and is given weekly as an injection form with monthly titration. Medication is discontinued if the patient loses < 5% weight after three months of treatment. The most frequent adverse effects include abdominal discomfort, headaches, fatigue, dyspepsia, disorientation, abdominal distension, eructation, hypoglycemia, increased heart rate, nausea, diarrhea, vomiting, and constipation. Patients also report Gastroenteritis and gastric reflux disease. When treating patients with a history of diabetic retinopathy, Semaglutide should be administered cautiously [41, 43]. Dulaglutide, the glucagon-like peptide-1 receptor agonist (GLP-1 RA) class has demonstrated efficacy in reducing weight, lowering blood sugar, and benefiting persons with T2D's CV in certain CV outcomes trials [53]. In the Award 11 trial patients escalated to dulaglutide 3.0 or 4.5 mg had further incremental weight reductions regardless of baseline BMI or HbA1c and were significantly more likely to achieve clinically important weight-loss thresholds and composite glycaemic and weight-control endpoints than patients treated with once-weekly dulaglutide 1.5 mg [54].

Non-FDA-approved drugs used in obesity include Metformin, Exenatide, and Setmelanotide. The FDA approves metformin to treat type 2 diabetes mellitus, and patients with metabolic syndrome, prediabetes, or insulin resistance have been treated with metformin as a first-line drug. A positive side effect of metformin is weight loss due to increased insulin sensitivity and decreased hepatic gluconeogenesis, and decreased glucose absorption from the intestine. Common side effects include gastrointestinal-related effects like nausea, vomiting, and diarrhea and are avoided in patients

with renal impairment due to the increased risk of lactic acidosis. Exenatide is a GLP1 analog approved by the FDA for treating type 2 diabetes mellitus with the positive side effect of weight loss. As a result, it is often used to treat obesity, for which it is still under trial and not yet approved. Setmelanotide has been given the FDA's Breakthrough Drug Designation for treating leptin-receptor-deficient obesity and obesity caused by POMC deficiency [43]. An open-label trial using bremelanotide investigated two patients with POMC deficiency. One person experienced a weight loss of 20.5 kg after 12 weeks of therapy, while the other experienced a weight loss of 51.0 kg after 42 weeks of therapy [48]. Dry mouth, localized skin induration at the injection sites, and darkening of skin nevi were among the side effects reported in the same trial. Despite these negative effects, Setmelanotide has demonstrated promise in treating childhood and adolescent obesity associated with genetics. Tirzepatide and Cotadutide, dual gastrointestinal peptide modulators of GLP-1 and either glucose-dependent insulinotropic polypeptide (GIP) or glucagon receptors, have phase 2 data suggesting efficient weight loss in particular groups [49]. Monoclonal antibody against skeletal myoblast activin type 2 receptors, Bimagrumab is a first-in-class innovative AOM. Its phase 2 trial concentrated on the endpoint of fat mass loss rather than total body weight loss [49-50]. In a phase 1 research, retatrutide, a single peptide having agonist action at the glucose-dependent insulinotropic polypeptide (GIP), GLP-1, and glucagon receptors, significantly reduced blood sugar levels and body weight [55]. And the American Gastroenterology Association recommendations were made by the guidelines panel. In people with overweight and obesity (body mass index 30 kg/m² or 27 kg/m² with weight-related comorbidities) who do not respond well to lifestyle therapies, the panel strongly advised using medication in addition to lifestyle change. Semaglutide 2.4 mg, liraglutide 3.0 mg, phentermine-topiramate ER, naltrexone-bupropion ER, and phentermine and diethylpropion (based on poor certainty evidence) were recommended by the panel for the long-term management of overweight and obesity. The advisory panel advised against using orlistat [52].

Lastly, certain drugs are undergoing a phase 2 clinical trial, such as Empathic™ (Bupropion in combination with Zonisamide) and Beloranib, and have shown a potential to get FDA approval [42, 51].

Table 1

Summary of the FDA-Approved Anti-Obesity Medications, their Mechanism of Action with Side Effects

Name	Mechanism of Action/ Clinical Effect	Side effect	Year approved
Phentermine (ADI PEX, LOMAIRA)	Sympathomimetic/Suppresses appetite	elevation in blood pressure and pulse, insomnia, constipation, and dry mouth	1959
Diethylpropion	Sympathomimetic/Suppresses appetite		1979
Orlistat (Alli, Xenical)	Intestinal lipase inhibitor/Reduces fat absorption	Orlistat may reduce the absorption of fat-soluble vitamins A, D, E, and K	1999
Phentermine-topiramate (Qsymia)	Combination sympathomimetic and carbonic anhydrase inhibitor/Decreases appetite and binge eating behaviors	paresthesias, dizziness, dry mouth, constipation, dysgeusia, insomnia, and anxiety, teratogen	2012
Bupropion-naltrexone (Contrave)	Combination of a dopamine and norepinephrine re-uptake inhibitor and mu-opioid receptor antagonist/ Decreases appetite and cravings	nausea/vomiting, constipation, headache, dizziness, insomnia, and dry mouth	2014
Liraglutide 3.0mg	GLP-1 receptor agonist/Decreases appetite, increases fullness, increases satiety	reversible increases in amylase/lipase activity, increase heart rate by an average of 2 beats/min	2014
Gelesis100 (Plenity)	Increases fullness	gastrointestinal, including abdominal distension, infrequent bowel movements, or dyspepsia.	2019
Setmelanotide (Imcivree)	Melanocortin-4-receptor agonist/ Decreases appetite	Injection site reactions, hyperpigmentation, and nausea.	2020
Semaglutide 2.4 mg (Wegovy)	GLP-1 receptor agonist/Decreases appetite, increases fullness, increases satiety	Serious adverse events included serious gastrointestinal disorders, hepatobiliary disorders, gallbladder disorders, mild acute pancreatitis	2021
Phentermine-topiramate (Qsymia)	People of age equal and greater than 12 with BMI in the 95th percentile or greater, standardized for age and sex	Paresthesias, dizziness, dry mouth, constipation, dysgeusia, insomnia, and anxiety, teratogen	2022

CONCLUSIONS

Obesity significantly affects the cardiovascular system, with increased mortality and morbidity worldwide. CVD is the leading cause of mortality worldwide, and obesity and overweight are significant modifiable risk factors for their development. Excess and abnormal adipose tissue contributes to an increased incidence of cardiovascular diseases by promoting hypercoagulable and hyperinflammatory states and significantly increasing the conventional CVD risk factors, including hypertension, atherosclerosis, diabetes mellitus, dyslipidemia, and metabolic syndrome. The increased prevalence of obesity because of its continuing obesogenic environment raises the burden of

cardiovascular diseases. Therefore, it is crucial to develop and implement effective obesity management interventions. Given the rising prevalence and disease burden, effective pharmacotherapeutic interventions are essential as adjuncts to lifestyle and surgical interventions to maintain weight loss and mitigate comorbidity risks. A comprehensive understanding of the pathophysiology underlying obesity has paved the way for developing and advancing several weight loss drugs with improved efficacy. Drug combinations targeting multiple complementary pathways have more potential to promote weight loss with minimal adverse effects. The decision regarding the appropriate medication is made considering the presence of comorbidities and risk factors, benefit to risk balance and adherence.

Obezitatea și excesul de greutate sunt factorii de risc majori pentru numeroase boli cronice, inclusiv bolile cardiovasculare, cum ar fi bolile de inimă și accidentul vascular cerebral, care sunt principalele cauze de deces la nivel mondial. Prevalența obezității a crescut dramatic atât în țările dezvoltate, cât și în cele în curs de dezvoltare, ceea ce o face o problemă semnificativă de sănătate publică și o criză globală. În ciuda faptului că modificările stilului de viață sunt tratamentul de primă linie, riscul ridicat de recădere a condus la un interes tot mai mare pentru intervențiile farmacologice neinvazive pentru a obține și menține pierderea în greutate și a scădea incidența obezității. Bolile cardiovasculare și cancerul reprezintă cele mai mari rate de mortalitate, printre alte comorbidități asociate cu obezitatea și excesul de greutate. Țesutul adipos în exces și anormal depus secretă diverși mediatori ai inflamației, ducând la boli cardiovasculare și cancer. Scăderea în greutate cu 5–10% reduce semnificativ riscul cardiometabolic. Medicamentele aprobate în prezent în SUA pentru gestionarea pe termen lung a obezității sunt orlistatul, naltrexona, bupropiona, fentermina/topiramatul și agonistii Glucagon Like Peptide-1 (GLP-1), cum ar fi liraglutida și semaglutida. Balanța risc/beneficiu al medicamentelor, comorbidităților și răspunsurilor individuale ar trebui să ghideze deciziile de tratament. Articolul oferă o privire de ansamblu cuprinzătoare și o discuție asupra mai multor medicamente de slăbit utilizate anterior și în prezent, inclusiv eficacitatea, mecanismele de acțiune și efectele secundare ale acestora.

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