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Pharmacological Treatment of Obesity: A Review of Current and Future Methods

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Abstract

Introduction and objective Obesity poses a significant public health challenge due to its association with an elevated risk of various chronic diseases, including cardiovascular conditions, type 2 diabetes, and overall mortality. While lifestyle modifications such as dietary changes and increased physical activity remain cornerstone interventions in obesity management, pharmacological treatments have emerged as an adjunctive approach to address this complex condition. The review aims to compare the effectiveness of current pharmacotherapy and show upcoming methods of treatment of obesity. Review methods The review was conducted by searching scientific publications in PubMed, Google Scholar, Clinicaltrials.gov, Summaries of Product Characteristics, URPL, FDA, and EMA databases. The articles on medications available in Poland for treating obesity and the latest clinical trials of upcoming drugs were analyzed, followed by a concise review of the collected data. Abbreviated description of the state of knowledge Currently, in the Polish market, medications available for obesity treatment include orlistat, the combination of naltrexone and bupropion, liraglutide, tirzepatide, and available as part of the target import - semaglutide. Promising clinical trials are being conducted on further medications for weight reduction, including retatrutide, orforglipron, cagrilintide, and amycretin. Regrettably, new and effective

medications due to their high cost and insufficient funding. Summary New pharmacotherapy options for obesity, particularly anti-diabetic medications, are rapidly advancing. Glucagon-like peptide-1 (GLP-1) analogs have shown promising results in weight reduction, surpassing previous medications such as orlistat or naltrexone. Recent drugs offer weight loss ranging up to 25%. More studies are underway on novel and increasingly effective medications.

Keywords :obesity, overweight, GLP-1 receptor agonist, SGLT2-inhibitors, obesity treatment, anti-obesity agents

Introduction and objective

Excessive or abnormal fat accumulation, presenting a health risk, is defined as obesity and overweight [1]. Depending on BMI, we distinguish:

• pre-obesity (BMI = 25-29.9 kg/m2);
• obesity class I (BMI = 30-34.9 kg/m2);
• obesity class II (BMI = 35-39.9 kg/m2);
• obesity class III (BMI ≥40 kg/m2) [2].

Environmental factors, primarily dietary habits and reduced physical activity, genetic factors, emotional disorders, eating disorders, hormonal imbalances, and certain medications play a role in the pathogenesis of obesity [3]. Excessive calorie intake contributes to increased lipid production, which may exceed the capacity of storage in adipose tissue and lead to ectopic deposition in other tissues, primarily in the liver and muscles. Consequently, there is a development of the inflammatory process in adipose tissue, the release of free fatty acids into the blood, and the development of insulin resistance – these are significant factors in the development of metabolic complications of obesity, such as 2 diabetes, and heart diseases [4]. Obesity has been linked to adverse effects on bone health and reproductive function, as well as an increased susceptibility to certain types of cancer. Moreover, it can significantly impact the quality of life, including sleep patterns and physical mobility [1].

According to the WHO, one in eight people worldwide suffered from obesity in 2022, between 1990 and 2022, the percentage of adults aged 18 and older suffering from obesity and overweight has more than doubled [1]. According to data from the Statistics Poland (Polish: Główny Urząd Statystyczny) in 2019, the percentage of individuals aged 15 and over with a BMI of 30 or higher in Poland was 18.5%, compared to 16.7% in 2014 [5]. This data underlines the substantial importance of the obesity problem in Poland and globally. Therefore, the acknowledgment of preventing overweight and obesity as Operational Objective 1 of Poland's National Health Program for 2021-25 is unsurprising. The program mainly focuses on nutrition and healthy lifestyle [6]. On the other hand, the treatment of obesity also includes pharmacotherapy. The objective of this review is to provide an overview of contemporary pharmacotherapy approaches and show new pathways for the treatment of obesity.

Review methods:

The review was carried out by conducting searches in scientific publications available on PubMed, Google Scholar, Clinicaltrials.gov, Summaries of Product Characteristics, URPL, FDA, and EMA databases. The analysis included articles concerning medications approved in Poland for obesity treatment and the most recent clinical trials investigating new drugs. Subsequently, a succinct summary of the gathered data was provided. The presented studies, which exceed the age of eight years, aim to briefly illustrate the effectiveness and mechanisms of action of drugs currently registered for obesity treatment.

Description of the state of knowledge:

In Poland's current market, there are several medications available for treating obesity, including orlistat, liraglutide, and the combination of naltrexone and bupropion. Recently, a new medication containing tirzepatide has also become available in Poland. Since October 2023, the targeted import of one drug with semaglutide to Poland has become possible. Other medications containing semaglutide are already available in Poland for treating type 2 diabetes [7]. The phase 2 trial results of a triple agonist of incretin hormone receptors GLP-1, GIP, and glucagon - retatrutide were presented in June 2023 in San Diego during the session of the American Diabetes Association [8]. Retatrutide exhibited a similar safety profile to other drugs based on nutrient-stimulated hormones but resulted in a weight loss of up to 24%. At the same congress, the results of a phase 2 study of the nonpeptide oral GLP-1 agonist, orforglipron, were

presented, which resulted in an average weight loss of 14.7% over the course of 36 weeks [9]. Other promising drugs in the treatment of obesity include cagrilintide and amycretin.

Orlistat

Orlistat (tetrahydrolipstatin) operates by inhibition of gastric and pancreatic lipase, thus diminishing fat absorption by around 30%. The indication for orlistat use includes a BMI ≥30 kg/m², a BMI ≥28 kg/m² combined with cardiovascular risk factors or obesity-related diseases and reducing the risk of weight regain after prior weight loss. The medication should be administered three times daily at a dosage of 120 mg, either immediately before, during or within an hour after a meal containing fat. When taken with a well-balanced diet and consistent physical activity, orlistat achieves its grandest efficacy. Potential reasons for terminating treatment could involve bothersome gastrointestinal disturbances and deficiencies in fat-soluble vitamins [10]. The effect of orlistat on weight reduction was assessed in the XENDOS trial. The administration of 120 mg of orlistat three times daily to obese patients with normal and impaired glucose tolerance resulted in an average reduction in body weight of 5.8 kg, compared to 3.0 kg in the placebo group after four years of observation. Furthermore, among patients taking orlistat, a 37.3% reduction in the incidence of type 2 diabetes was demonstrated. Furthermore, the study found that combining orlistat with lifestyle changes resulted in lasting improvements in cardiometabolic risk factors. It is worth noting that only 52% of individuals taking orlistat completed the trial, compared to 34% taking the placebo [11].

Naltrexone/Bupropion

Naltrexone, used for the treatment of alcoholism and opioid dependency, functions as a potent opioid antagonist, selectively targeting central nervous system opioid receptors. Bupropion, an antidepressant, exerts its effects by inhibiting the reuptake of dopamine and noradrenaline, thus leading to decreased appetite and reduced food intake. The combination of bupropion and naltrexone utilizes the synergistic effects of both drugs. These centrally acting medications are believed to exert their mechanism of action by targeting the arcuate nucleus of the hypothalamus. Bupropion enhances the production and release of α-MSH from POMC pathway cells in the hypothalamus, leading to an increased feeling of satiety. Blocking the μ-opioid receptor by naltrexone enables bupropion to prolong the activation of POMC neurons [12]. Naltrexone/bupropion is an adjunctive therapy combined with a reduced-calorie diet with

increased physical activity in patients with a BMI ≥30 kg/m² or a BMI ≥ 27 kg/m2 to < 30 kg/m2 combined with at least one obesity-related disease. The dosing regimen is gradually escalated as follows: one tablet daily is administered in the initial week, followed by two tablets daily in the second week, three tablets daily in the third week, and four tablets daily from the fourth week onwards. The most common adverse reactions include nausea, constipation, vomiting, dizziness, dry mouth, and headache. Bupropion undergoes metabolism by cytochrome P450 to produce its primary active metabolite, creating the possibility of interactions with other medications [13]. The efficaciousness of combining naltrexone with bupropion in reducing body weight has been estimated in randomized, placebo-controlled clinical trial. The participants underwent lifestyle modifications and were randomized into three groups in a 1:1:1 ratio. The first group was administered a combination of naltrexone at 32 mg and bupropion at 360 mg daily, the second group received a combination of naltrexone at 16 mg and bupropion at 360 mg daily, whereas the third group received a placebo orally twice daily for 56 weeks. The mean reduction in body weight among patients receiving the naltrexone 32 mg plus bupropion group was 6.1%, 5.0% in the naltrexone 16 mg plus bupropion group, whereas in the placebo group 1.3% over 56 weeks. The advantages of using the drug encompassed a decrease in waist circumference, an enhanced insulin sensitivity, a reduction in triglyceride levels, and an elevation in HDL cholesterol levels. In individuals diagnosed with depression, bupropion has a potential to induce suicidal thoughts and behaviors; nevertheless, no suicide attempts or completed suicides were reported in the conducted trial [14].

Liraglutide

Liraglutide is a glucagon-like peptide-1 (GLP-1) receptor agonist, which, by binding to the GLP-1 receptor, stimulates insulin secretion, decreases blood glucose levels, enhances satiety, and reduces appetite. Liraglutide is registered for the treatment of obesity and type 2 diabetes as an adjunctive therapy combined with a reduced-calorie diet with increased physical activity in patients with a BMI ≥30 kg/m² or a BMI ≥ 27 kg/m2 to < 30 kg/m2 combined with at least one obesity-related disease. The treatment should be initiated at a dose of 0.6 mg once daily subcutaneously, followed by gradual dose escalation of 0.6 mg/day each week until reaching the therapeutic dose of 3 mg once daily or the maximum tolerated dose. The gastrointestinal tract is the primary site of adverse reactions, with symptoms such as nausea, vomiting, and diarrhea being the most frequently reported [15]. The efficacy of liraglutide in reducing weight was assessed in randomized, double-blinded, placebo-controlled Phase III clinical trials. In the

SCALE Obesity & Pre-Diabetes trial, participants included obese or overweight individuals and at least one comorbidity, excluding diabetes. Administering liraglutide subcutaneously once daily at a dosage of 3.0 mg, in conjunction with lifestyle modifications, led to an average weight loss of 8.0±6.7% compared to 2.6±5.7% in the placebo group over 56 weeks. Furthermore, liraglutide induced better glycemic control, reduced arterial pressure and other cardiometabolic risk factors also enhanced quality of life [16]. The SCALE Diabetes trial also demonstrated the effectiveness of liraglutide. Overweight or obese patients with type 2 diabetes were administered subcutaneous liraglutide at doses of 3.0 mg, 1.8 mg, and placebo once daily, with weight loss of 6.0% (3 mg), 4.7% (1.8 mg), and 2.0% (placebo), respectively [17].

Semaglutide

Semaglutide is a GLP-1 analogue that regulates appetite, calorie intake and diminishes preference for high-fat foods by activating the GLP-1 receptor. It regulates insulin and glucagon secretion based on blood glucose levels. Semaglutide demonstrates a favorable impact on the cardiovascular system, inhibiting atherosclerosis development and exerting anti-inflammatory effects, thereby positively influencing blood lipid levels, and reducing systolic blood pressure. Semaglutide has been registered in Poland for obesity treatment in patients with a BMI ≥30 kg/m² or a BMI ≥ 27 kg/m2 to < 30 kg/m2, in combination with at least one obesity-related condition through targeted import. The dosing regimen commences with a subcutaneous administration of 0.25 mg weekly, gradually increasing to 2.4 mg over 16 weeks. The most common adverse reactions reported concern gastrointestinal disorders, such as: nausea, diarrhea, constipation, and vomiting [18]. The efficacy of semaglutide in reducing weight was assessed in four randomized, double-blinded, placebo-controlled Phase IIIa clinical trials (STEP1-4) [19,20,21,22]. All participants were overweight or obese and underwent lifestyle modifications. In the STEP 1 trial individuals without diabetes were randomly assigned to two groups: one receiving once a week subcutaneous semaglutide 2.4 mg and the other receiving a placebo in a 2:1 ratio. After 68 weeks, patients receiving semaglutide achieved a mean weight reduction of 14.9% (-15.3kg) compared to 2.4%(-2.6kg) in the placebo group [19]. In the STEP 2 trial individuals with type 2 diabetes were randomly assigned to three groups: one receiving weekly subcutaneous semaglutide at a dose of 2.4 mg, another receiving semaglutide at a dose of 1 mg, and a third receiving a placebo for 68 weeks. The mean weight loss was 9.6% (- 9.7kg) for semaglutide 2.4 mg, 7.0% (-6.9kg) for semaglutide 1.0 mg, and 3.4% (-3.5kg) in the placebo group [20]. In the STEP 3 trial participants were subjected to behavioral counseling, a highly

restrictive diet, and increased physical activity. Patients were randomly assigned to groups receiving subcutaneous injections of 2.4 mg semaglutide once weekly or placebo. After 68 weeks, the mean weight loss was 16% (-16.8kg) for semaglutide and 5.7% (-6.2kg) in the placebo group [21]. In the STEP 4 trial, all participants were administered weekly injections of 2.4 mg semaglutide for 20 weeks. Afterward, they either continued receiving semaglutide treatment or switched to the placebo group for 48 weeks. The participants receiving semaglutide sustained weight loss (-7,9%), while those in the placebo group experienced a gradual weight gain (+6,9%). After the trial concluded, the average weight in the placebo group remained lower than at baseline but higher than that of the individuals treated with semaglutide. Participants administered semaglutide exhibited superior improvements in metabolic risk factors and a major increase in participant-reported physical functioning from baseline compared to individuals receiving placebo. The adverse events primarily involved the gastrointestinal tract, with occurrences such as nausea, constipation, and diarrhea [22].

The observations from STEP-HFpEF and SELECT trials have pivotal importance in elucidating the potential cardiological benefits of pharmacological combating obesity. The STEP-HFpEF trial findings were released in August 2023. Obese patients with symptomatic heart failure with preserved ejection fraction were assigned to groups receiving once-weekly 2.4 mg of semaglutide or placebo for 52 weeks. Patients receiving semaglutide achieved greater mean weight loss (-13.3%) as well as reduction in heart failure symptoms and improvement in quality of life compared to placebo [23]. At the end of 2023, the results of the SELECT trial were published. This study involved patients who were overweight or obese, had preexisting cardiovascular disease, but did not have diabetes. They received once-weekly subcutaneous injections of either semaglutide at a dose of 2.4 mg or a placebo. Individuals receiving semaglutide experienced an average weight loss of 9.4%, but more notably, they also saw a 20% reduction in cardiovascular risk [24].

Tirzepatide

Tirzepatide is an agonist of incretin hormone receptors - both GLP-1 (glucagon-like peptide-1) and GIP (glucose-dependent insulinotropic polypeptide). Tirzepatide diminishes energy intake and appetite by enhancing sensations of satiety and fullness while reducing sensations of hunger. It heightens the sensitivity of pancreatic β-cells to glucose. It augments insulin secretion during both the first and second phases in response to glucose levels. Tirzepatide is registered for the treatment of obesity as an adjunctive therapy combined with a reduced-calorie diet with

increased physical activity in patients with a BMI ≥30 kg/m² or a BMI ≥ 27 kg/m2 to < 30 kg/m2 combined with at least one obesity-related disease. The dosing regimen initiates with a 2.5 mg once-weekly dose, with an escalation to 5 mg once weekly after four weeks. Subsequently, if necessary, the dosage can be increased at intervals of at least four weeks by 2.5 mg up to a maximum dose of 15 mg once weekly. The most common adverse events include gastrointestinal disturbances such as nausea, diarrhea, constipation, and vomiting [25]. Tirzepatide initially received registration for treating type 2 diabetes. However, in November 2023, the FDA expanded its approval to encompass therapy for obesity [26]. The phase III clinical trial program SURMOUNT assessed the effectiveness of tirzepatide in reducing body weight in individuals with obesity or overweight [27,28,29,30]. In the SURMOUNT-1 trial overweight or obese patients without diabetes but with at least one weight-related complication were administered once a week subcutaneous tirzepatide at a dose of 5 mg, 10 mg,15 mg, or placebo for 72 weeks. The overall average weight reduction was about 16% (-16.1kg) for a dose of 5mg, 21,4% (-22,2kg) for a dose of 10mg, 22,5% (-23,6kg) for a dose of 15mg and 2,4%(-2,4kg) for placebo. Most patients with prediabetes achieved normoglycemia (95.3% for tirzepatide vs. 61.9% for placebo) [27]. In the subsequent trial, SURMOUNT-2, individuals with a BMI of 27 kg/m2 or greater and glycated hemoglobin levels ranging from 7 to 10% were randomized to receive either subcutaneous tirzepatide once a week at a dosage of 10mg or 15 mg or placebo for 72 weeks. The overall average weight reduction was about 12.8% (10 mg), 14.7% (15 mg), and 3.2% (placebo) [28]. In October 2023, the results of the SURMOUNT-3 trial were published. Patients who were obese or overweight and had at least one obesity-related complication, except diabetes, were included. Throughout the study period, patients followed a diet and physical activity regimen. The trial investigated the impact of tirzepatide on the dose of 10 or 15 mg or placebo once weekly for 72 weeks on weight loss following a successful intensive lifestyle intervention. Participants, who had already lost 6.9% of their initial body weight through conventional diet and activity counseling, experienced an additional 18.4% weight loss when treated with tirzepatide, in contrast to a gain of 2.5% observed in those assigned to the placebo group [29]. In the subsequent SURMOUNT 4 trial all participants initially received subcutaneous tirzepatide once weekly for 36 weeks. Afterward, they were randomized into two groups: one continuing tirzepatide and the other receiving a placebo for 52 weeks. After the tirzepatide initiation period, patients achieved a weight loss of 20.9%. In the subsequent stage, participants who continued tirzepatide treatment additionally achieved a 5.5% weight loss (26.0% from the baseline throughout the entire 88-week period), while the

placebo group experienced a weight gain of 14% [30]. The results of SURMOUNT-3 and SURMOUNT-4 provide evidence contradicting the belief that individuals with obesity or overweight can sustain their weight loss solely through diet and exercise. It should be noted that tirzepatide administration led to improvements in cardiometabolic risk factors. The adverse events related to the gastrointestinal tract were the most frequently reported and usually of mild to moderate severity. Tirzepatide demonstrated better glycemic control and weight loss outcomes than semaglutide, due to its more effective reduction of glycated hemoglobin levels. The ongoing SURMOUNT-5 trial, which compares tirzepatide and semaglutide, is expected to confirm this fact [31].

Retatrutide

Retatrutide acts as an agonist of the glucose-dependent insulinotropic polypeptide (GIP) receptor, the glucagon-like peptide-1 (GLP-1) receptor, and the glucagon receptors [32]. The medication has undergone evaluation in phase II trials up to now [32,33]. In the trial published in The New England Journal of Medicine (NEJM), obese or overweight patients, with obesity-related conditions other than diabetes, were randomized to groups receiving subcutaneous retatrutide once weekly in doses of 1 mg, 4mg (with initial dose of 2 or 4 mg), 8mg (with initial dose of 2 or 4 mg), 12 mg (with initial dose, 2 mg) or placebo. The most effective weight reduction was attained by all participants who received 8 mg or 12 mg of retatrutide, as observed in the trial. Individuals administered the maximum dosage of retatrutide experienced an average weight decrease of 24.2% after 48 weeks. This timeframe did not fully exploit the drug's effects, suggesting that continued use would likely yield additional benefits [32]. In The Lancet, a phase II clinical trial was published demonstrating that retatrutide, in addition to weight loss, also results in better glycemic control in patients with type 2 diabetes. Participants were randomized to four groups receiving subcutaneous retatrutide once weekly in doses of 0.5, 4, 8, and 12 mg. In the 4 mg dose group, certain participants started treatment with a 2 mg dose, which was subsequently increased to 4 mg. Similarly, some participants in the 8 mg dose group experienced either gradual (from 2 to 4 to 8 mg) or rapid dose escalation (from 4 to 8 mg). The comparative group consisted of patients treated with either placebo or dulaglutide at a dose of 1.5 mg. After 36 weeks, the average weight loss in patients treated with the highest dose of retatrutide was 17%. In both trials, retatrutide administration led to improvements in cardiometabolic risk factors. The gastrointestinal tract was the site of the most common adverse effects of retatrutide [33]. The phase 2 trials results are promising as participants continued to

lose weight at the end of the study, comprehensive assessment of efficacy and tolerance in the obesity pharmacological therapy will be possible in the ongoing phase 3 trials (TRIUMPH 1-4) [34,35,36,37].

Orforglipron

The mechanism of action of orforglipron involves agonistic binding to the GLP-1 receptor. It is a non-peptide drug administered orally. In the phase II clinical trial published in The New England Journal of Medicine (NEJM), obese or overweight patients with obesity-related conditions other than diabetes were randomized to groups receiving orforglipron at doses of 12, 24, 36, or 45 mg or placebo once daily for 36 weeks. In the 26th week, a reduction in body weight was observed, ranging from 8.6% to 12.6% in the treatment groups and 2% in the placebo group. By the 36th week, this percentage increased to a range of 9.4% to 14.7% for orforglipron and 2.3% for placebo [38]. The subsequent study published in The Lancet, assessed the efficacy of orforglipron at a dose of 3, 12, 24, 36, or 45 mg in treating type 2 diabetes compared to a placebo and dulaglutide at a dose of 1,5 mg. After 26 weeks, the mean body weight decreased by up to 10.1 kg with orforglipron compared to 3.9 kg with dulaglutide and 2.2 kg with placebo. The safety profile of orforglipron resembled that of other GLP-1 receptor agonists, moreover, gastrointestinal side effects were the most frequently reported adverse events [39]. Phase III trials are underway to assess the safety and effectiveness of orforglipron in treating chronic obesity [40,41].

Amylin analogues

Amylin is a hormone secreted by pancreatic β cells in response to food intake. It regulates gastrointestinal function by reducing appetite and slowing gastric emptying. Cagrilintide is a pharmaceutical compound targeting the amylin receptor. A phase 2 trial evaluated the safety and effectiveness of combined cagrilintide and semaglutide (CagriSema) in obese or overweight patients with type 2 diabetes. The trial randomly assigned participants to receive once-a-week subcutaneous injections of CagriSema, semaglutide, or cagrilintide. The dose was escalated to 2.4 mg for all drugs. The average weight loss for CagriSema was -15.6%, which yields a comparable effect to tirzepatide [42]. In the ongoing phase 3 trial using Cagrisema (REDEFINE), a weight reduction of up to 25% is expected [43]. The oral amylin receptor agonist, amycretin, induced a 13% reduction in weight over 12 weeks in a phase 1 trial [44]. In comparison, the drug containing semaglutide (Wegovy) caused a weight loss of 6% after 12

weeks. The promising outcomes warrant further phase 2 and 3 clinical trials investigating amycretin.

Summary

The development of new pharmacotherapy approaches for obesity, especially focusing on anti-diabetic medications, is rapidly progressing. Treatment outcomes depend on the duration, dosage, and drug characteristics. The first glucagon-like peptide-1 (GLP-1) analogs were confirmed to effectively reduce body weight by approximately 5%, surpassing the weight loss observed with previously used medications like orlistat or naltrexone. Recently developed drugs offer the potential for weight loss ranging from several to as much as 25% of body weight. Retatrutide is likely to be as effective due to its interaction with three receptors influencing appetite, whereas tirzepatide interacts with two receptors and semaglutide with one receptor. A combination of two incretin analogs, CagriSema, may have an additive synergy and is a promising drug. Among the medications currently available on the Polish market for obesity, tirzepatide appears to be the most effective. Limitations to its application may involve the necessity for weekly injections, adverse effects predominantly affecting the gastrointestinal system, and the treatment cost. When selecting the most appropriate medication, it is essential to consider the patient's existing health conditions, potential drug interactions, adverse reactions, and their preferences for medication dosage and form.

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