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Pharmacological treatment of obesity: an overview of different groups of anti-obesity drugs available in Poland

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Abstract

Introduction and Objective: Obesity, as one of the diseases of civilization, has become a significant problem in our time. Although the first ways of treating it appeared many years ago, pharmacotherapy of obesity has been developing significantly in recent years.

The purpose of this article is to introduce the obesity drugs that have been registered for the treatment of obesity in Poland and to describe a new substance called tirzepatide, which, although it does not have such registration yet, is one of the most promising medications of the near future.

State of Knowledge: Obesity is an urgent and growing problem. In Poland, about 25% of adults are obese, and this number is increasing over the years. [1] [2]

In Europe, four drugs belonging to three different groups are registered for the treatment of obesity: orlistat, a combined drug that includes naltrexone hydrochloride and bupropion hydrochloride, liraglutide, and semaglutide. Although the last drug achieves the best results in studies and is the substance most favored by doctors and patients, there is still much research on new substances and formulations, which would bring even better results and health benefits. One of these substances is tirzepatide, a drug registered in 2022 for the treatment of type 2 diabetes.

Summary: Nowadays in Poland, there are four drugs registered for obesity. Two of them are representatives of the group of GLP-1 analogues.

Pharmacological treatment of obesity has good results and is a relatively safe process that should be implemented in conjunction with lifestyle changes. The fifth substance described in

this article is tirzepatide, a drug that, although not registered for the treatment of obesity yet, is for now one of the most promising substances among the new drugs.

Keywords: Anti-obesity agents; GLP-1 receptor agonists; weight loss; overweight; obesity; healthy lifestyle.

Introduction

Obesity and overweight are now alarming problems affecting child and adult populations.

Worldwide, more than 1 million people suffer from obesity, and the number continues to grow. Excess body weight leads to dangerous complications and serious diseases, which include cardiovascular diseases, metabolic syndrome, sleep apnea, and also cancer. [3] [4]

As a result, the treatment of obesity has become one of the most important goals of our time. Thanks to the revolutionization of treatment and the introduction of new drugs into widespread use, this has become possible.

According to the definition provided by the World Health Organization overweight and obesity are characterised by abnormal or excessive fat accumulation that presents a health risk. A body mass index (BMI) over ≥25 kg/m2 is considered overweight, and BMI ≥ 30 kg/m2s is described as obesity. [5]

The problem of obesity affects many parts of the world and it is a growing concern in both developed and developing countries. [5] In a 1980-2015 study, researchers collected data from 68.5 million children and adults from more than 195 countries and territories. They observed that the prevalence rate of obesity has doubled in ≥70 countries and has been continuously increasing, causing 4.0 million deaths, two-thirds of deaths were due to cardiovascular disease. [6]

The treatment of obesity and overweight should always begin with changing eating habits, reducing daily calorie intake, introducing physical activity of appropriate intensity, and setting goals for therapy. These non-pharmacological methods should always form the basis

of treatment. Pharmacotherapy should only be considered in patients who, despite following the above recommendations, do not achieve a specific therapeutic goal and have a BMI of ≥30 kg/m2. Such management also refers to those with a BMI ≥27 kg/m2 and the coexistence of ≥1 obesity-related disease, and in the case of adolescents aged ≥12 years, with a body weight over 60 kg and with obesity diagnosed with cutoff points defined by the international standard (according to the International Obesity Task Force criteria). [7]

When deciding whether to introduce treatment with drugs, the patient should be assessed holistically in terms of cardiovascular risk, the coexistence or development of other diseases, complications of obesity, and preferences concerning the drug administration route.

Treatment of obesity should be conducted under the guidance of specialists and weight reduction must be gradual. Otherwise, too rapid weight loss can lead to serious complications, such as electrolyte disturbances, arrhythmia, hyperuricemia, gallstones, or mood disorders. [3]

The pharmacotherapy for obesity should last at least 6 months, and the optimal time is ≥12 months. Treatment should be gradual and aimed at achieving goals. The effectiveness of a drug can be measured through a reduction in baseline body weight by ≥5% over a 3-month period of taking the drug at the therapeutic dose.

If pharmacotherapy proves ineffective in addressing obesity, exploring non-pharmacological interventions becomes imperative.

It is advisable to refrain from concurrent usage of multiple drugs. In the event of inadequate response, the option of transitioning to an alternative medication may be considered.

Types of drugs used in weight reduction

According to the recommendations of the European Medicines Agency (EMA), four drugs, belonging to three different pharmaceutical groups, are currently registered for the treatment of obesity. These drugs are orlistat, the combination formula of naltrexone hydrochloride and bupropion hydrochloride, liraglutide, and semaglutide. [7]

Orlistat

Orlistat is the oldest drug among those registered for the treatment of obesity. It is used in the form of oral tablets. Its action is based on inhibiting gastric and pancreatic lipases, which prevents the breakdown of triglycerides into a form absorbable by the human body, resulting in the reduction of fat absorption by up to 30%. [8] [9]

A study was performed on 80 obese patients who were divided into two groups: one receiving 120 mg of orlistat three times a day and the other receiving a placebo at the same frequency. Individual parameters and measurements were taken at the beginning of the study in the 8th, 16th, and 24th weeks. The study not only showed that orlistat led to a reduction in body weight, and waist circumference, but also showed decreased levels of total cholesterol and low-density lipoprotein (LDL) cholesterol. [8] [10]

in Poland, orlistat is predominantly regarded as a third-line medication due to its significant side effects, particularly gastrointestinal issues such as diarrhea, steatorrhea, fecal spotting, abdominal pain, and anal fissures. However, it's crucial to note that the intensity of orlistat's side effects typically diminishes with continued therapy.. [...]Rarely, orlistat is associated with cholelithiasis, pancreatitis, and acute cholestatic hepatitis.

Moreover, among the three groups of anti-obesity drugs, orlistat is the least effective in reducing weight.[7]

Due to its mechanism of action, orlistat inhibits the absorption of fat-soluble nutrients such as vitamins, and this may contribute to deficiencies in these vitamins. However, according to the drug's product characteristics, during the four-year study, the levels of vitamins A, D, E, K, and beta-carotene remained within normal limits in most patients. Nevertheless, both doctors and patients need to prioritize a well-balanced diet that includes products rich in essential vitamins. In instances where multivitamin supplements are taken, it is advisable to supplement at least two hours after taking orlistat or before bedtime. This ensures optimal absorption and effectiveness while minimizing potential interactions. [11]

The medication composed of naltrexone hydrochloride and bupropion hydrochloride

A second drug intended for the treatment of obesity consists of two active substances - naltrexone hydrochloride and bupropion hydrochloride - both exerting central effects. Previously, these substances were known and used in monotherapy for indications other than obesity treatment. Bupropion was utilized in the treatment of nicotine addiction and depression [12], while naltrexone, registered for monotherapy, is used in the treatment of opioid and alcohol addiction. [13]

These substances exhibit different mechanisms of action. Naltrexone presents antagonistic effects primarily against μ-opioid receptors and, to a lesser extent, against κ and δ receptors. Bupropion, however, is a selective norepinephrine-dopamine reuptake inhibitor (NDRI) with

minimal impact on serotonin reuptake and without inhibiting monoamine oxidase. [14] Additionally, it also acts as a non-competitive antagonist of nicotinic receptors. [15]

Through the synergistic action of both substances, specifically the process of hyperadditive synergy, this two-component preparation has found application in obesity treatment. The precise mechanism of action of these substances has not been fully elucidated though. Both substances influence two areas of the brain: the arcuate nucleus of the hypothalamus, where hunger and satiety centers are located, and the mesolimbic dopaminergic reward system. One theory suggests that the success of the synergy lies in bupropion increasing the feeling of satiety, while naltrexone reduces food intake by affecting the reward center in the brain. [16] [15]

There are two neurotransmitters involved in the feeling of satiety: POMC (proopiomelanocortin) and CART (cocaine amphetamine-related transcript). Bupropion stimulates the release of POMC and CART. These neurotransmitters, in turn, stimulate the release of α-MSH (alpha-melanocyte-stimulating hormone), which induces a feeling of satiety by binding to specific receptors. Furthermore, proopiomelanocortin leads to the release of β-endorphin which blocks the activity of neurons releasing POMC through negative feedback loop receptors. Naltrexone influences the removal of this blockade, thereby prolonging the feeling of satiety and supporting the action of bupropion. Moreover, a commercial medication named Mysimba®, composed of these two substances, affects appetite. Through the mechanism of action of bupropion and naltrexone, stimulation of the reward system occurs, leading to a reduction in food intake to satisfy the pleasure sensation. [15]

GLP-1 agonists: liraglutide and semaglutide

Glucagon-like peptide-1 (GLP-1) is an incretin hormone produced in the small intestine and in the distal part of the colon, released in response to a meal. The development of GLP-1 analogs has significantly advanced the treatment of type 2 diabetes and obesity.

GLP-1 agonists, a group of drugs that mimic the action of endogenous GLP-1, offer various benefits during their use. By imitating the natural hormone, these drugs enhance insulin secretion, slow down gastric emptying, reduce appetite, increase the feeling of satiety, and thereby contribute to weight loss. Additionally, these medications have protective effects on blood vessels, the heart, and the liver, reducing the risk of cardiovascular events. They lower

blood pressure, increase diuresis and sodium excretion in urine, and improve endothelial function. [17]

For some time, the only GLP-1 analog registered for obesity treatment in Poland was liraglutide. Until 2023, semaglutide was used off-label for weight loss, but this changed after the registration of the drug in injection form under the trade name Wegovy®. [14]

The advantage of semaglutide over liraglutide lies not only in its efficacy but also in the frequency of drug administration. Semaglutide can be taken once weekly via subcutaneous injection or daily as an oral tablet in the form of a peptide complex with salcaprozate sodium [18], whereas liraglutide requires daily subcutaneous injections.

Among GLP-1 agonists, semaglutide has been subject to numerous clinical trials to assess its effectiveness, with one of the latest being the STEP program, a series of studies demonstrating the drug's efficacy in treating excess weight in individuals without type 2 diabetes (excluding STEP 2). [19]

In the STEP 8 trial, comparing the effectiveness of semaglutide with liraglutide, patients were treated for 68 weeks. The liraglutide group experienced an average weight reduction of 6.4%, while the semaglutide group achieved a significantly higher average weight loss of 15.8%. [19]

Semaglutide has proven to be the most effective medication to date. Studies have shown its positive impact on various factors related not only to obesity but also its complications. This GLP-1 analog positively influences blood pressure, lipid metabolism, glycated hemoglobin levels, and leads to a reduction in waist circumference. It is generally well-tolerated by patients, with common side effects including gastrointestinal disturbances such as diarrhea, nausea, and vomiting, typically reported in the initial months of therapy.

Recent reports have raised concerns about the adverse effects of GLP-1 analogs, specifically an increased risk of gastroparesis, pancreatitis, biliary disease, bowel obstruction, and acute pancreatitis. [20] According to the product characteristics of Wegovy®, doctors should inform their patients about these potential adverse effects, and in case of confirmed pancreatitis, the treatment with semaglutide should be discontinued and not resumed after diagnosis. [21]

In summary, when using GLP-1 agonists, it is essential to be aware of these rare adverse effects and communicate them to the patient. Regular monitoring and prompt intervention in case of adverse events are crucial for the safe and effective use of these medications.

Tirzepatide

Tirzepatide, although not registered for obesity treatment and not yet available in Poland, is worth mentioning. This new medication, used to lower blood glucose levels in adults with type 2 diabetes, received FDA (Food and Drug Administration) approval in May 2022 and EMA (European Medicines Agency) approval in November of the same year.

Tirzepatide, a polypeptide and the first representative of its group introduced into treatment, acts as a GLP-1 agonist and also as an agonist for glucose-dependent insulinotropic polypeptide (GIP) receptors. This dual mechanism involves the activation of two different types of receptors [22]. Tirzepatide slows down gastric emptying (this effect diminishes with subsequent doses) and increases insulin secretion from pancreatic β cells, while simultaneously blocking glucagon secretion. Additionally, it contributes to weight loss, enhancing metabolic control, which is crucial in type 2 diabetes therapy. The medication's benefits include increased satiety, decreased cravings for sweet and/or high-fat food, and increased energy expenditure. [22]

Due to its weight loss effect, a series of studies were conducted. In July 2022, the results of the SURMOUNT-1 study were officially published. The study involved 2539 adults without diabetes, with a BMI equal to or greater than 30 or a BMI equal to or greater than 27 with at least one complication related to being overweight. The trial included administering the medication along with the adoption of healthy dietary habits and physical activity. After 72 weeks, there was an average weight loss correlated with the tirzepatide dose (5mg, 10mg, 15mg), resulting in 15%, 19.5%, and 20.9%, respectively. Meanwhile, the placebo group showed a weight loss of 3.1%. [23]

In the study-phase 3 trial-SURPASS 2-, in which the effectiveness of tirzepatide was compared with the widely used semaglutide in 1879 individuals with type 2 diabetes, it was proved that tirzepatide was more efficient. After 40 weeks of drug use, the average weight loss for semaglutide (1 mg) was 6.7%, while for tirzepatide, it ranged from 8.5%, 11%, 12.4% depending on the dosage (5, 10, and 15 mg).

However, it is important to note that the dose of semaglutide that was used in this study is not the approved anti-obesity dose, which should be 2.4 mg weekly. [24] [25]

Tirzepatide, as a dual agonist of GLP-1 and GIP receptors, has demonstrated efficacy in maintaining normal blood glucose levels in people with confirmed effectiveness in those with type 2 diabetes. [22]

Conclusions:

In conclusion, with the increasing prevalence of obesity, the popularity of medications for this condition is likely to continue to rise. The positive results of currently registered drugs indicate their efficacy and safety. However, ongoing research persists in the quest for new drugs that hold the potential to be even more effective. It is crucial to emphasize that patient education, focusing on the significance of specialist care, the role of physical activity, and maintaining a balanced diet in weight reduction, should be integrated with pharmacotherapy to enhance overall treatment outcomes.

Author contributions

Conceptualization, BW and ML; methodology, IM and MK ; software, not applicable; check, KS, IM, BW and DB; formal analysis, DB, MK, IM and KS; investigation, MK and PP; resources, not applicable; data curation, IM, PP, ML, BW; writing - rough preparation, BW; writing - review and editing, BW, DB, MK and ML; visualization, DB, PP, KS; supervision, BW; project administration, ML; receiving funding, not applicable.
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