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The Worldwide Problem of Obesity - Comparison of the Effectiveness of Pharmacological Treatment with Semaglutide and Tirzepatide in Reducing Body Weight

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ABSTRACT

Introduction

Obesity is a disease that has been affecting an increasing number of people in the last decade. In addition to surgical and dietary treatment, pharmacological treatment plays an important role in its treatment. Obesity is a risk factor for many diseases, including cardiovascular disease and diabetes, and increases the risk of mortality, which is why appropriate treatment is so important. Comparison of pharmacological treatment methods using two preparations from the group of GLP-1 analogues, such as semaglutide and tirzepatide, available for prescription use in European Union countries, may help select the most effective therapy tailored to the patient.

Aim of the body

The aim of the study was to summarise and compare the two preparations available for use by patients in terms of their mode of action and their impact on body weight reduction.

Methods and Materials

The following keywords were used to review the literature available in the PubMed database: "obesity", "semaglutide", "tirzepatide", "weight loss after semaglutide treatment", "weight loss after tirzepatide treatment" and "treatment of obesity". We also used literature available in other scientific journals, literature available on Google Scholar and data collected and stored by WHO.

Keywords

Obesity treatment, Ozempic, Semaglutide, Mounjaro, Tirzepatide, Body weight loss, GLP-1 analogues, Obesity

Introduction

In recent years, both in Poland and globally, there has been a consistent increase in the number of individuals struggling with overweight and obesity, affecting not only adults but also children and adolescents. Obesity is a pathological accumulation of fat tissue, which causes a disruption in the proper functioning of the body in various areas of life. This condition significantly elevates the risk of developing other diseases and experiencing premature mortality.[1] Since 1990, the global prevalence of obesity among adults has more than doubled. By 2022, 2.5 billion people worldwide were classified as overweight, including nearly 890 million affected by obesity. According to data collected by the World Health Organization (WHO), in 2022 every eighth person worldwide suffered from obesity.[2]

A body mass index (BMI) above the normal range was responsible for nearly 5 million deaths in 2019. These deaths were associated with obesity-related diseases, such as cardiovascular diseases, diabetes, chronic respiratory conditions, and digestive system disorders.[3] The constantly growing number of obesity cases worldwide correlates with an increase in the incidence of obesity-related diseases and a lower age at which these diseases begin to appear.[4]

When analyzing obesity, attention should be paid to its etiopathogenesis and the type of obesity occurring in the patient. We can divide obesity according to the etiopathogenesis of its occurrence into primary obesity and secondary obesity. Primary obesity, also known as alimentary obesity, is caused by a positive energy balance in the patient, i.e. an excessive supply of calories concerning the real demand of the body. Environmental factors play the most important role in this type of obesity. Most often, it is the consumption of highly processed food, which is a source of excessive amounts of simple carbohydrates and contains a high content of trans fats. Environmental factors that contribute to the occurrence of this type of obesity also include limited physical activity. This type of obesity is the most common among the population. According to studies, 98% of children who were diagnosed with obesity have primary obesity. [5,6] The second type of obesity is secondary obesity occurring in the course of endocrine diseases such as hypothyroidism, Cushing's disease and syndrome, hypogonadism, and deficiency of somatotropin, also known as growth hormone. It may also appear in the course of genetically determined syndromes (Prader-Willi syndrome, Turner syndrome, Klinefelter syndrome) and during chronic pharmacotherapy with certain

medications (glucocorticosteroids, phenothiazine derivatives, antidepressants, antiepileptic drugs, insulin, and others). [5]

An additional important aspect in the case of obesity is the phenomenon of excessive growth of the number of adipocytes and an increase in their volume. The increase in fat cells occurs only during puberty, which, in the case of excessive occurrence of this phenomenon, may be responsible for the development of obesity already in puberty and its further progression in adulthood, because the process of increasing the number of adipocytes is irreversible. [7,8]

Obesity is a growing problem, which raises concerns about the development of new pharmacological treatments. Data provided by the WHO shows that in 1990, only 2% of children and adolescents aged 5-19 suffered from obesity, which was about 31 million people, but by 2022, the natural ten covered up to 8%, including as many as 160 young people, which is why new methods of treating obesity are so important. [2]

Materials and Methods

The study was written based on literature available on platforms such as PubMed and Google Scholar. ResearchGate, ClinicalTrials, FDA, and data analyzed by the World Health Organization (WHO) were also used. In the study, we refer to drugs approved for use by the Food and Drug Administration (FDA) and the European Medicines Agency (EMA). The collected data were analyzed for obesity and weight loss during its treatment.

Pharmacotherapy for obesity

Pharmacotherapy is a method of treating obesity that is used in Poland in patients with a body mass index (BMI) ≥30 kg/m2, in whom, as a result of dietary and behavioral treatment, no significant reduction in body weight has been achieved and therapeutic goals have not been achieved. Pharmacotherapy aimed strictly at reducing body weight can also be used in overweight patients with a BMI ≥27 kg/m2 and the coexistence of ≥1 obesity-related disease. Obesity-related diseases include: carbohydrate metabolism disorders (including prediabetes and diabetes), hypertension, dyslipidemia, obstructive sleep apnea, and cardiovascular diseases (CVD). [9] The group of patients eligible for pharmacological treatment of obesity also includes adolescents over 12 years of age whose body weight exceeds 60 kilograms and whose obesity has been diagnosed following international standards, taking into account the

criteria of the International Obesity Task Force (IOTF), which define obesity based on the BMI value adjusted for the patient's age and gender. In the treatment of obesity in adolescents over 12 years of age, drugs such as liraglutide and semaglutide are allowed. [9]

The aim of pharmacological treatment of obesity is not only to reduce body weight but also to alleviate symptoms or complete remission of diseases accompanying this disease. This therapy additionally helps reduce the risk of other health complications related to obesity. [9]

Currently, there are 5 drugs approved by the EMA for treating obesity in the European Union. These include orlistat, a drug combining naltrexone hydrochloride and bupropion hydrochloride, and GLP-1 analogues: liraglutide, semaglutide, and tirzepatide. [9,10,11] As of December 2024, three drugs were registered in Poland for the treatment of obesity: orlistat, a drug combining naltrexone hydrochloride and bupropion hydrochloride, and one GLP-1 analogue called liraglutide at a dose of 3.0 mg. [10,11]

Tab. 1 . Obesity drugs approved for use by EMA [9, 11, 13]

Name (Trades Names)	**Mechanism of Action**	**Clinical Effect**
Approved for the treatment of obesity in Poland and in the UE by EMA (as of December 2024)		
Orlistat (Xenical)	Intestinal Lipase Inhibitor	Reduces fat absorption up tp 30%
Naltrexone hydrochloride and bupropion hydrochloride (Mysimba)	Inhibits the neurochemical mechanisms responsible for the feeling of hunger	Decreases appetite and cravings
Liraglutide 3.0 mg (Saxenda)	GLP-1 receptor agonist	Decreases appetite, increases fullnes, increases satiety
Others substances approved for the treatment of obesity by EMA (as of December 2024)		
Semaglutide 2.4mg (Wegovy)	GLP-1 receptor agonist	Decreases appetite, increases fullnes, increases satiety
Tirzepatide	GLP-1 and GIP receptor dual agonist	Decreases appetite, increases fullnes, increases satiety

Obesity treatment is a process that lasts not weeks but can usually last for years because obesity is a chronic disease with no tendency to go away on its own. According to the recommendations of the Polish Society for the Treatment of Obesity (PTLO), therapy should last at least 12 months. It should also be individually tailored to the patient's needs, considering the set goals and the pace of weight loss, which depend on the patient's initial weight and medical history. [9]

GLP-1 and GIP analogues

The hormone produced by enteroendocrine cells of the intestines in response to an increase in glucose levels after a meal is glucagon-like peptide 1 (GLP-1). GLP-1 is responsible for stimulating insulin secretion, inhibiting glucagon secretion, and delaying gastric emptying, which causes a feeling of satiety and reduces appetite. Thanks to this mechanism, synthetic analogues of GLP-1 can help reduce calories intake and promote weight loss, making it a key element of modern obesity therapies. [13,14]

GLP-1 affects the brain and in particular, the reward system, reducing the feeling of pleasure associated with eating. This action goes beyond simple appetite control, which suggests the potential of GLP-1 in treating binge eating disorders. In a study by scientists from Rutgers University (USA), a mouse model showed that reducing GLP-1 levels led to an increased appetite and a preference for high-fat foods. However, increasing the concentration of this hormone caused a decrease in interest in fatty foods, and the animals began to eat smaller meals and less frequently.[13]

It should be remembered that any substance can cause side effects, which is also the case with GLP-1 analogues. Among the side effects, we can mention those originating from the digestive system:

- nausea
- vomiting
- diarrhea.

These symptoms can appear throughout the treatment, but they occur much more often as the drug doses are increased.[14]

To reduce the side effects associated with the use of GLP-1 analogues and increase the effectiveness of pharmacotherapy, a combination of a GLP-1 analogue with glucose-

dependent insulinotropic polypeptide (GIP) was developed. GIP is an incretin hormone, a 42-amino acid polypeptide naturally produced by the mucosa of the small intestine, specifically the endocrine K cells located in the duodenum. It is worth emphasizing that GIP supports lipid and glucose metabolism, translating into additional health benefits for patients. [15,16]
In a 2004 study on mice, the human GIP receptor gene was isolated and a knockout mouse study was conducted. The results indicated that the absence of the GIP receptor correlated with obesity in the mouse population. [16]

Semaglutide

Semaglutide, a synthetic analogue of glucagon-like peptide-1 (GLP-1), works by activating the GLP-1 receptor, which is located in various organs.[21]
Semaglutide is a relatively new substance on the pharmaceutical market. In 2017, semaglutide, as an active substance, was approved for medical use by the FDA in the United States. It should be noted that it was registered for the pharmacological treatment of obesity by the EMA in January 2022.[20,24] According to analyses, it has become one of the most popular drugs in the US, taking 48th place on the list of most prescribed drugs in the US in 2022. It is estimated that this accounts for about 13 million prescriptions.[25]
Regarding chemical structure, semaglutide shows 94% homology with human GLP-1. However, it differs in the lack of the first six amino acids in human GLP-1. In addition, amino acids are swapped at positions 2 and 28 - alanine is replaced with 2-aminoisobutyric acid and lysine with arginine. The drug becomes resistant to degradation by the enzyme dipeptidyl peptidase-4 by replacing lysine. [26]
In addition, the ability of semaglutide to bind to albumin in the blood is increased by attaching a chain containing 18 carbon atoms and a carboxyl group to lysine at position 20. Such chemical modifications extend the drug's half-life in the blood, which is from 165 to 184 hours, or about 7 days. Due to these minor structural changes, semaglutide is characterized by a long-lasting effect.[27]
This allows for convenient administration of the drug once a week in the form of a subcutaneous injection or once a day in the form of an oral tablet.[21]
Semaglutide has a multifaceted effect, including regulation of blood glucose levels and weight loss support, making it an effective and versatile agent in treating type 2 diabetes and obesity.[20,21,22] It also has a blood pressure-lowering effect and a positive effect on lowering LDL cholesterol, vLDL cholesterol, and triglycerides.[18]

Semaglutide is approved in the US, the European Union, the UK, and Canada for weight management in eligible individuals at a dose of 2.4 mg once weekly as a subcutaneous injection. [17]

Among the side effects that may occur when using semaglutide are nausea and diarrhea, which occur very often, i.e. in more than 1 patient in 10. Additionally, you can mention vomiting, abdominal pain, gastritis, increased lipase activity, increased amylase activity, weight loss, etc. These symptoms appear often, i.e. in more than 1 patient in 100 and less than 1 in 10 patients. [17, 20,24]

The phase 3 STEP 5 study was designed to evaluate the efficacy and safety of semaglutide 2.4 mg compared with placebo in adults with obesity or overweight with at least one weight-related comorbidity but without diabetes. Both groups received behavioral support during the 104-week study. The study included 304 participants. Using the ITT principle, participants were randomly assigned to equal groups of 152. 282 participants (92.8%) completed the study, defined as attending the end-of-study and safety visit. Only 272 subjects completed weight checks at the end of the study in week 104, of whom 243 (79.9%) remained in therapy at the end-of-study visit. [18]

At the end of Phase 3 of the STEP 5 study, the mean estimated change in body weight from baseline to week 104 was -15.2% in the semaglutide group and -2.6% in the placebo group. [18] At week 104 of the study, participants treated with semaglutide were significantly more likely to achieve at least a 5% weight loss compared with the placebo group. This goal was achieved by 77.1% (111 participants) of those taking semaglutide, compared with only 34.4% (44 participants) of those taking placebo. [18]

Tirzepatide

Tirzepatide is a peptide that simultaneously acts on the GLP-1 and GIP receptors. In terms of its chemical structure consists of 39 amino acids, which can be compared to the structure of GIP enriched with a functional group, thanks to which the duration of action of tirzepatide was extended. Thanks to this structure, the substance, like semaglutide, can be administered in subcutaneous injections once a week. [28]

Tirzepatide, in terms of its mechanism of action, shows an affinity for the GIP receptor, which can be compared to naturally occurring GIP. Regarding affinity for the GLP-1 receptor, the substance shows 5 times lower affinity than native GLP-1. [28]

Tirzepatide, sold under Mounjaro, obtained marketing authorization in the European Union on September 15, 2022. [29] Previously, on May 13, 2022, it was approved by the U.S. Food and Drug Administration (FDA) as a treatment for type 2 diabetes. Additionally, on November 8, 2023, the FDA approved tirzepatide under the name Zepbound for the long-term treatment of weight management in adults who are obese or overweight and have at least one condition associated with excess body weight. [30]

Like semaglutide, tirzepatide has various side effects. The most frequently reported (in ≥1/10 patients) were nausea and diarrhea. Common side effects (in more than 1 in 100 but less than 1 in 10 patients) included dizziness, hypotension, abdominal pain, vomiting, dyspepsia, and others. Hair loss was also reported as a common side effect, especially in overweight or obese individuals, regardless of the presence of type 2 diabetes. [29]

In 52 research centers and hospitals located in India, Japan, Mexico, and the USA, a study called SURPASS-1 was conducted, the aim of which was to assess the efficacy of tirzepatide and its safety and tolerability by patients during the use of this drug as monotherapy. The effect of tirzepatide was compared with the placebo group. [31] The study lasted 40 weeks, from June 2019 to Oct 2020, and involved 478 randomly assigned to 4 study groups. The groups assigned to tirzepatide consisted of 121 people, which constituted 25% of all study participants in each group. The first group took tirzepatide at a dose of 5 mg, the second 10 mg, and the third 15 mg. The fourth group, the control group taking a placebo, consisted of 115 people, which constituted 24% of the study participants. The average age of patients participating in the SURPASS 1 study was 54 years. 52% of the study participants were male. Another important aspect is that 66 participants, 14% of the study group, discontinued the study drug. 50 people finished their participation before the end of the study. [29,31]

After 40 weeks of the SURPASS-1 study, the tirzepatide group experienced a dose-dependent weight loss of 7.0 to 9.5 kg. The adverse events reported by the study participants were mild to moderate and were of short duration. The most reported adverse events included gastrointestinal problems such as nausea (12-18% vs. 6% in the placebo group), diarrhea (12-14% vs. 8%), and vomiting (2-6% vs. 2%). There were no treatment-related episodes of hypoglycemia among the study participants. [31]

Another clinical trial called SURMOUNT1 was designed to test the effectiveness of tirzepatide in weight loss in obese and overweight patients. The study included 2,539 adults with a BMI of 30 or more and 27 or more with at least one condition related to excess body weight, excluding diabetes. The study was randomized, controlled, and similar to SURPASS 1, divided the subjects into 4 groups. Three groups received tirzepatide at doses of 5 mg, 10

mg, and 15 mg. The fourth group received a placebo. The entire study lasted 72 weeks, including a 20-week dose escalation period. Patients taking tirzepatide started on a dose of 2.5 mg for 4 weeks. The dose of tirzepatide was then increased by 2.5 mg every 4 weeks until they reached their assigned dose. The average age of the patients was 45 years. 67.5% of the study participants were female. The mean baseline body weight was 104.8 kg, and the mean BMI was 38 kg/m2. [32]

Like SURPASS 1, adverse events related to tirzepatide were reported in SURMOUNT-1. Most adverse events were gastrointestinal, mild to moderate in severity, and occurred primarily during dose escalation. Adverse events were discontinued in 4.3%, 7.1%, 6.2%, and 2.6% of participants receiving tirzepatide 5 mg, 10 mg, 15 mg, and placebo, respectively. [32]

At week 72, significant weight loss was observed in the tirzepatide arm: -15.0% for 5 mg, -19.5% for 10 mg, and -20.9% for 15 mg, compared to -3.1% for placebo. The proportion of participants with a weight loss of at least 5% was 85% (5 mg), 89% (10 mg), and 91% (15 mg), compared to 35% in the placebo group. In addition, 50% and 57% of participants in the 10 mg and 15 mg doses achieved a weight loss of at least 20%, compared to 3% in the placebo group. Tirzepatide also improved all cardiometabolic parameters analyzed. Both studies showed that tirzepatide was effective in reducing body weight in obese patients and in those with at least one disease associated with excess body weight. [32]

Conclusion

The comparison of semaglutide and tirzepatide underscores the significant strides made in pharmacological obesity treatments, with both drugs demonstrating notable efficacy in weight reduction. Semaglutide offers a well-established approach with robust clinical support, while tirzepatide introduces the added advantage of dual receptor action, potentially amplifying its impact on weight loss. However, the choice between these agents must consider individual patient characteristics, including comorbidities, side effect profiles, financial considerations, and personal preferences.

Although medications like semaglutide and tirzepatide have proven to be effective tools in the treatment of obesity, they should not be viewed as standalone solutions. Sustainable outcomes require combining pharmacotherapy with comprehensive lifestyle modifications, including dietary changes, physical activity, behavioral interventions, and social support. Such an

integrated approach is essential for achieving long-term success, as it addresses weight loss and the broader health challenges associated with obesity.

These findings underline the importance of continued research to explore these therapies' long-term safety, effectiveness, and cost implications. Expanding access to such treatments remains a critical priority, ensuring that all individuals, regardless of socioeconomic status, can benefit from advancements in obesity management. Future studies and long-term follow-up will be necessary to evaluate further these drugs' relative benefits, safety, and cost-effectiveness. Nevertheless, the drugs we compare represent a significant advance in the pharmacological treatment of obesity, giving hope to patients struggling with this chronic disease.

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