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Pharmacotherapy for overweight and obesity: past and current clinical practice, available medications and possible applications

Farmakoterapia nadwagi i otyłości: historia, praktyka kliniczna, dostępne preparaty i możliwe zastosowania

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Abstract

Overweight and obesity are a global pandemic that continues to escalate year by year. Also in Poland, there is a steady increase in the prevalence of overweight and obesity cases among both adults and children. The most effective methods for treating these conditions include improved dietary habits and increased physical activity. Pharmacotherapy is another treatment option. Psychological care is also proven to be effective. It is important to note that in Polish primary health care settings, practitioners are unable to prescribe free dietary consultations for patients. Due to limited visit time, it can be challenging to monitor whether patients have implemented the required lifestyle changes. Primary medical care is often the first point of entry for overweight and obese patients seeking treatment. Consequently, pharmacotherapy has become a crucial aspect of overweight and obesity treatment. In recent decades, many appetite-suppressing medications have been withdrawn from the market because of serious side effects. On the other hand, new medications have been approved for sale in recent years or even months. All indications are that the trend will continue. This article includes a description of both historically used and currently approved overweight and obesity medications, both in the European Union and in the USA. For each medication, the mechanism of action, efficacy, and potential adverse effects are described.

Keywords: obesity pharmacotherapy, obesity medications, overweight, weight reduction, obesity

Streszczenie

Występowanie nadwagi i otyłości to pandemia o zasięgu globalnym, która z roku na rok staje się coraz większym problemem. W Polsce również zauważalny jest wzrost liczby osób z nadwagą lub otyłością. Ten problem dotyczy zarówno populacji dorosłych, jak i dzieci. Podstawa leczenia nadwagi i otyłości to leczenie żywieniowe oraz aktywność fizyczna. Innym sposobem leczenia nadwagi i otyłości są środki farmakologiczne. Istotne znaczenie ma również postępowanie psychologiczne. W warunkach podstawowej opieki zdrowotnej nie ma możliwości zlecenia bezpłatnej dla pacjenta konsultacji żywieniowej, a z powodu ograniczonego czasu trwania wizyty trudno zalecić i monitorować adekwatną modyfikację stylu życia. Warto zauważyć, że gabinet podstawowej opieki zdrowotnej jest często jedynym miejscem, w którym pacjent może się dowiedzieć, jak ważne jest zapobieganie nadwadze i otyłości, a także ich leczenie. W obecnej sytuacji warto zwrócić uwagę na farmakoterapię nadwagi i otyłości. W ostatnich dekadach wiele leków zmniejszających apetyt zostało wycofanych z powodu działań niepożądanych. Z drugiej strony w ciągu ostatnich kilku lat, a nawet miesięcy obserwujemy dopuszczanie do sprzedaży nowych środków do leczenia nadwagi i otyłości. Wszystko wskazuje na to, że ten trend będzie się utrzymywał. W artykule omówiono kilka leków historycznie wykorzystywanych w leczeniu nadwagi i otyłości, a także opisano leki zarejestrowane do stosowania w tym wskazaniu w Stanach Zjednoczonych i w Unii Europejskiej. W opisie leków skupiono się na ich mechanizmie działania, skuteczności i działaniach niepożądanych.

Słowa kluczowe: leczenie farmakologiczne otyłości, leki na otyłość, nadwaga, obniżenie masy ciała, otyłość

INTRODUCTION

The World Health Organization (WHO) defines obesity as abnormal or excessive accumulation of fat in the body that presents a risk to health[1]. In 1948, the WHO classified obesity as a disease and included it in the International Classification of Diseases (ICD)[2]. In 1995, the WHO announced that overweight and obesity posed a greater public health concern than malnutrition[1]. The body mass index (BMI – kg/m^2) is an easily accessible and commonly used indicator for assessing overweight and obesity. Overweight is defined as a BMI value of 25–29.9 kg/m^2, while obesity is defined as a BMI ≥30 kg/m^2[2,3]. Excessive adipose tissue disrupts various physiological functions in the human body, adversely affecting metabolism and mechanics, and imposing strain on other organs. Metabolic effects of obesity are driven by increased insulin resistance and disturbances in adipokine secretion, leading to chronic inflammation and energy imbalances. Clinical consequences include prediabetes, type 2 diabetes, dyslipidaemia, cardiovascular diseases (hypertension, coronary artery disease, atherosclerosis), numerous cancers, and infertility in both women and men[4]. Beyond metabolic effects, excessive fat tissue mechanically disrupts healthy physiological functions, causing conditions like gastroesophageal reflux disease, hiatal hernia, impaired lung ventilation including obstructive sleep apnoea, and joint degeneration. In their 2016 study, Smith and Smith state that approximately 2.1 billion people worldwide are overweight or obese. Obesity is identified as the fifth leading cause of global mortality, resulting in nearly 3.4 million deaths annually[3]. These data underscore the serious health implications of overweight and obesity. Therefore, several questions arise: What triggers overweight and obesity? How can overweight and obesity be prevented? What are the effective treatments for these conditions? Based on review articles and recommendations from the Polish Society for Obesity Management (Polskie Towarzystwo Leczenia Otyłości, PTLO), the primary causes of obesity include increased intake of calorie-dense foods (particularly high in fats and simple sugars) and decreased levels of physical activity. While genetic, socioeconomic, and certain medication-related factors can also increase the risk of obesity, they do not play the leading role in its development[3,5,6]. In a time when highly processed, calorie-rich foods are readily available and affordable, people often struggle to accurately determine which foods are calorie-dense. After consuming a high-energy meal, the body fails to differentiate it from a standard-energy meal, resulting in overconsumption of calories. This mechanism is termed passive overeating[5]. One possible approach to address this issue is treatment with appetite-suppressing medications.

TREATMENT OF OVERWEIGHT AND OBESITY

According to the latest PTLO recommendations, initial treatment for overweight and obesity should focus on nutritional therapy, psychological support, and increased physical activity[6]. The foundation of nutritional therapy is prolonged reduction of the total calorie content in the diet. The PTLO recommends a hypocaloric diet, involving an energy intake reduction of 500–600 kcal in relation to requirements. In practice, this entails a diet with an energy content of 1,200–1,500 kcal/day for women and 1,500–1,800 kcal/day for men. The diet should be properly balanced in terms of nutritional components. For instance, the PTLO states that a Mediterranean diet should provide 15–18% kcal/day from protein, 35–45% kcal/day from fats, 35–45% kcal/day from carbohydrates, and a minimum of 18–38 g of fibre per day[6]. Overweight and obese individuals are advised to engage in regular physical activity (≥30–60 minutes of exercise ≥5 times per week). Aerobic exercise is the most recommended type. Strength training is also necessary for maintaining and increasing lean body mass (especially muscle). Since individuals with overweight and obesity typically have low activity levels, they should start with low-intensity exercise and gradually increase the intensity over time. Obese individuals, especially those not achieving treatment goals or requiring support for implementing healthy lifestyle changes, should receive psychological care. In primary care settings, introducing all the aforementioned recommendations is challenging due to limited visit time and lack of opportunities to refer patients for free consultations with dietitians, psychologists or physiotherapists. Therefore, attention should be paid to the potential of pharmacotherapy for managing overweight and obesity. The PTLO recommends pharmacotherapy for obesity in combination with a calorie-restricted diet and increased physical activity for patients who have not achieved a significant weight reduction (≥5% of initial body weight) through dietary and behavioural measures within 3–6 months. Another indication for pharmacotherapy combined with lifestyle changes (diet and physical activity) is overweight in patients with a BMI ≥27 kg/m^2, who have not responded to non-pharmacological measures and have ≥1 comorbid condition (prediabetes, diabetes, hypertension, obstructive sleep apnoea, dyslipidaemia). Moreover, pharmacotherapy is recommended for adolescents aged ≥12 years with a body mass >60 kg and a diagnosis of obesity[6]. These recommendations are grounded in the fact that dietary interventions and lifestyle changes alone are insufficient for achieving long-term weight reduction. In the 2006 study, Foster noted that without consistent supervision, obese patients typically regain about a third of their lost weight within a year. The majority of patients return to their previous weight after five years[7]. For physicians prescribing pharmacotherapy to overweight and obese patients in order to achieve better weight control, the following principles are important:

- **Pharmacotherapy for overweight and obesity is long-term and potentially indefinite due to the chronic nature of the condition**. The PTLO recommends that pharmacotherapy should last no less than six months, with an optimal treatment duration of ≥12 months[6].

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- **Pharmacotherapy for overweight and obesity improves both weight control and the management of concomitant diseases**. In the treatment of overweight and obese patients, addressing and preventing obesity-related diseases is crucial. Clinical trials have demonstrated that semaglutide and liraglutide, drugs belonging to the glucagon-like peptide-1 (GLP-1) analogue group, reduce cardiovascular risk[8–11].
- **Patient responses to treatment can vary significantly**. Diet and physical activity remain important. Appetite-suppressing medications have a stronger effect on weight reduction when combined with lifestyle changes (i.e. dietary modifications and increased physical activity)[6].

HISTORY OF PHARMACOTHERAPY FOR OVERWEIGHT AND OBESITY

Over the years, pharmacotherapy for overweight and obesity has encompassed various drugs from different groups. Selected pharmacotherapeutic agents, most of which have been withdrawn from the market, are discussed below. The aim is to provide a historical and contemporary review of pharmacotherapy options for overweight and obesity.

The first appetite-suppressing drugs were developed in the 1940s in the USA. The first such medication was the amphetamine derivative dextroamphetamine (methamphetamine). In subsequent years, other amphetamine derivatives, such as phentermine and amfepramone, were marketed[12,13]. Phentermine combined with topiramate (an antiepileptic drug) is currently approved for overweight and obesity treatment in the USA[14]. Amphetamine derivatives induce a strong and rapid anorectic effect, but they are addictive and associated with serious adverse effects (myocardial infarction, pulmonary hypertension, myocardial fibrosis)[13,15]. In 1962, the Kefauver–Harris Act was passed in the USA, requiring, among other things, a demonstration of the benefits outweighing the risks of drugs introduced to the market[12]. The Act led to the withdrawal of many drugs with unproven efficacy, including many amphetamine derivatives.

Fenfluramine is another stimulant substance introduced for obesity treatment in the USA in 1959. Fenfluramine was marketed under various trade names, including Pondimin. Combined with phentermine (another amphetamine derivative), it was sold as Fen-Phen[12,13]. Fenfluramine works by increasing serotonin release through alterations in serotonin transporters[16]. When combined with phentermine, fenfluramine acts on both the serotonergic and dopaminergic systems, increasing the levels of both monoamines. Both fenfluramine and the fenfluramine–phentermine combination exhibit strong anorectic effects. The majority of weight reduction occurs within the first 2–4 weeks of drug use, and gradual weight loss continues for 6–9 months of treatment. Fenfluramine and fenfluramine–phentermine combinations are known to have an addictive potential. Adverse effects include tachycardia, hypertension, stroke, heart attack, sleep disturbances, agitation, tremors, and dry mouth. In 1997, Fen-Phen, the most popular medication containing fenfluramine, was withdrawn from the market due to numerous cases of heart valve disease in patients taking the drug[13]. Currently, fenfluramine is approved by the European Medicines Agency (EMA) under the brand name Fintepla as an antiepileptic drug[17].

Mazindol (Mazanor, Sanorex) is a drug introduced in the 1960s. It also is a stimulant and produces similar effects to amphetamine, elevating blood pressure and decreasing appetite. Mazindol works by increasing the reuptake of norepinephrine, and to a lesser extent, dopamine and serotonin. It exhibits a very strong anorectic effect, especially in the initial weeks of use. An average weight loss of about 12 kg was observed within two months of treatment[18]. Mazindol induces many adverse effects, including dangerous spikes in blood pressure, sleep disturbances, tremors, tachycardia, tachypnoea, panic attacks, aggression, and seizures. Mazindol was withdrawn from the market in most countries by the end of the 20th century[18].

Rimonabant (Acomplia, Zimulti) is an agonist/partial agonist of CB1 cannabinoid receptors. The drug affects both central and peripheral cannabinoid receptors. It reduces appetite and has a beneficial impact on lipid profiles. Rimonabant allowed patients to achieve a weight reduction ranging from 5% to 10% compared to their initial weight[19]. The drug was withdrawn in 2009 due to an increased risk of psychiatric adverse effects including anxiety disorders, depression, and suicidal ideation[19,20].

Sibutramine (Meridia) was introduced to the market in 1997. It works by inhibiting the reuptake of serotonin and norepinephrine, reducing appetite. The drug had a strong anorectic effect. In treated patients, weight loss ranged from 6.1% to 7.4% compared to 1.2% in the placebo group[21]. Sibutramine was withdrawn from the market in 2010 due to cardiovascular-related deaths in patients taking the drug[21,22]. Sibutramine and its derivatives are added to dietary supplements called "fat burners", which is an illegal practice[23].

CURRENT POSSIBILITIES OF PHARMACOTHERAPY OF OVERWEIGHT AND OBESITY

Orlistat (Xenical) is the longest-standing medication on the market for the treatment of obesity. It was introduced to the European market by the EMA in 1998, while the Food and Drug Administration (FDA), the institution responsible for controlling and approving drugs in the USA, approved the medication in 1999. Orlistat is a partially hydrogenated, synthetic analogue of lipostatin – an irreversible inhibitor of pancreatic lipase[24]. Orlistat inhibits the hydrolysis of triglycerides into free fatty acids and reduces their absorption from the digestive tract by approximately 30%. In double-blind placebo-controlled studies, it was statistically shown that orlistat had significantly greater efficacy

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in reducing body weight compared to placebo. The average weight loss in patients treated with orlistat for 12 months is about 3%[24]. Therapy with orlistat in combination with a low-fat diet may potentially interfere with the absorption of fat-soluble vitamins (A, D, E, K). Common adverse effects include abdominal pain, flatulence with discharge, urgency to defecate, fatty stools, and frequent bowel movements. Rare adverse effects include liver damage, acute pancreatitis, and acute renal failure[24].

Lorcaserin (Belviq) is a medication approved by the FDA, which has been available in the USA since 2012, but the EMA did not grant approval for its use in the European Union. The drug is a selective agonist of serotonin 5-HT2C receptors[25] which are mainly located in the hypothalamus, and their activation leads to an increased release of pro-opiomelanocortin (POMC) in the arcuate nucleus. POMC, in turn, affects the hypothalamic paraventricular nuclei, leading to the release of alpha-melanocyte-stimulating hormone, which reduces appetite[25,26]. In clinical studies, after one year of follow-up, the group of patients using lorcaserin lost an average of 5% to 5.8% of body weight compared to 2.2% to 3.6% in the placebo group[25,26]. The most common adverse effects of the medication include headache, dizziness, fatigue, and nausea. Also, caution should be exercised because of an increased frequency of hypoglycaemia in patients with diabetes. Lorcaserin is a serotoninergic drug, so its use is associated with the risk of serotonin syndrome. Also, it should not be combined with other serotoninergic medications.

Liraglutide (Saxenda) was approved by the FDA in 2014, and the EMA authorised the medication for the European market in 2015. Originally, the drug was registered under the brand name Victoza and indicated for treating type 2 diabetes[27]. In a higher dose, it was registered under the trade name Saxenda for the treatment of obesity (BMI ≥30 kg/m^2) and overweight (BMI ≥27 kg/m^2) in patients with at least one obesity-related comorbidity[8]. Liraglutide belongs to the class of GLP-1 analogues[8,27]. GLP-1 receptors are present in both the central nervous system (CNS) and the gastrointestinal system. Liraglutide increases satiety and delays gastric emptying. In clinical trials using a 3 mg dose for 12 months, an average weight loss of 5.9% to 8% was observed compared to the placebo group, where an average weight loss of 0.2% to 2.6% was noted[8–10,28]. Common adverse effects of liraglutide include nausea, vomiting, diarrhoea, constipation, hypoglycaemia, headache, decreased appetite, and dyspepsia. During clinical trials, isolated cases of acute pancreatitis occurred. Liraglutide is contraindicated in patients with a personal or family history of medullary thyroid carcinoma[28].

Phentermine and topiramate (Qsymia) is a medication that was approved by the FDA in 2012 for treating obesity and overweight, but it did not receive a positive opinion from the EMA. Phentermine is an amphetamine derivative, while topiramate is an antiepileptic drug whose mechanisms of action are not fully understood. Proposed target points of topiramate include voltage-dependent sodium channels, voltage-dependent potassium channels, GABA-A receptors, and AMPA receptors[14]. The combination of these substances has a very strong and rapid anorexigenic effect. In a clinical study involving patients treated with phentermine and topiramate for 56 weeks at the full dose, an average weight loss of 9.8% was observed compared to 1.2% in the placebo group. Furthermore, an improvement in the lipid profile and a reduction in systolic blood pressure were observed. Common adverse reactions included typical responses to stimulating (sympathomimetic) substances, such as dry mouth, headache, insomnia, nervousness, constipation, palpitations, tachycardia, and elevated blood pressure. It was also demonstrated that the combination of phentermine and topiramate could induce metabolic acidosis[14].

Naltrexone/bupropion (Mysimba, Contrave) in an extended-release tablet form is a medication approved by the FDA and the EMA in 2014 for the treatment of obesity and overweight[29]. Naltrexone is an opioid receptor antagonist, while bupropion is an antidepressant belonging to the group of selective norepinephrine–dopamine reuptake inhibitors (NDRI). It is suspected that the anorexigenic effect of the combination of naltrexone and bupropion is due to their impact on dopamine pathways in the hypothalamus and the mesolimbic system. The effect of the medication is to decrease appetite, enhance the feeling of fullness, and increase the resting energy expenditure[29]. In clinical trials, an average weight loss of 8.1% to 11% was demonstrated in patients receiving the medication for 56 weeks, compared to an average weight loss of 1.4% to 7.3% in patients receiving a placebo. Patients who lost the most initial body weight participated in a study involving behavioural therapy in combination with pharmacotherapy[29]. The most common adverse effects of the naltrexone/bupropion combination are nausea, constipation, headache, and vomiting.

Semaglutide (Wegovy) is the newest medication approved for obesity treatment. It was registered by the EMA in January 2022 for the treatment of obese (BMI ≥30 kg/m^2) and overweight (BMI ≥27 kg/m^2) patients with at least one obesity-related comorbidity. The medication has also been approved for the same indication by the FDA. Currently, Wegovy is not available in Poland, but other formulations containing semaglutide are registered for the treatment of type 2 diabetes (Ozempic and Rybelsus). Semaglutide, approved for overweight and obesity treatment (Wegovy), is available in a subcutaneously injected solution form. Another medication with the same active substance in an oral form is also available (Rybelsus), but it is not registered for overweight and obesity treatment. Semaglutide is another medication belonging to the group of GLP-1 analogues. The medications were initially developed for treating type 2 diabetes, and clinical studies have shown that they can also lead to weight loss in patients. Medications in this group increase endogenous insulin synthesis and decrease glucagon release, which has a positive effect on carbohydrate metabolism (i.e. improves glycaemic control). The weight

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loss effect is likely due to the direct influence of GLP-1 analogues on the hypothalamus and other CNS structures, as well as delayed gastric emptying. A significant portion of patients participating in clinical trials achieved a weight loss of 5% or more[11]. Besides weight reduction, semaglutide has been found to have cardioprotective effects. The most common adverse effects associated with the drug are nausea and vomiting[11].

CONCLUSIONS

Pharmacotherapy for the management of overweight and obesity is a rapidly evolving field. Over the past decades, numerous pharmacological agents have been marketed and withdrawn from the market. In recent years, and even months, we have witnessed the introduction of new pharmacological agents, and this trend is expected to continue. The latest medications, belonging to the GLP-1 analogues group (semaglutide and liraglutide), exhibit high efficacy and a range of additional benefits. It can be speculated that these medications could potentially curb the obesity epidemic on a large population scale. They have the potential to positively impact therapeutic goals and improve the quality of life for patients suffering from overweight or obesity. However, these medications are quite expensive, and the financial barrier may impede access for many patients.

Conflict of interest

The authors do not declare any financial or personal connections with other individuals or organisations that could negatively affect the content of the publication and claim the right to this publication.

Author contributions

Original concept of study: PSW. Collection, recording and/or compilation of data: PSW, MW, GP. Analysis and interpretation of data: PSW, MW, GP. Writing of manuscript: PSW, MW, GP. Critical review of manuscript: PSW, MW, GP. Final approval of manuscript: PSW.

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