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Pharmacotherapy of obesity — state of the art

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Abstract

Obesity, which affects about 13% of the world population, results in significant deterioration of health and serious clinical, mainly metabolic and cardiovascular complications. Although the basis of therapeutic treatment is behavioural treatment, often non-pharmacological effects do not produce the desired effect. Currently there are several drugs with a safe action profile that improve the effect of treatment (5–10% weight reduction). The aim of the paper is to present the potential of modern pharmacotherapy in the treatment of obesity, in terms of mechanism of action, efficacy, and side effects, in order to individualise therapy. The drugs already registered include substances with a variety of mechanisms of action, including phentermine, orlistat, lorcaserin, and liraglutide. Compounded preparations (phentermine/topiramate, naltrexone SR/bupropion SR) are also available, which, by using low doses of active substances, have beneficial effects while reducing side effects. In addition, several drugs used to treat diabetes, such as metformin, SGLT2 inhibitors, GLP-1 agonists, and pramlintide, promote weight loss, although their use is reserved for diabetics, especially type 2 patients. Regarding the current alarming epidemiological data there is a need for intensive prevention and treatment of obesity as well as the development of a new form of pharmacotherapy (new substances and treatment regimens) to develop effective, safe, and, above all, long-term effective therapy for the treatment of obesity. **(Endokrynol Pol 2018; 69 (4): 448–457)**

Key words: *obesity, pharmacotherapy, phentermine, orlistat, lorcaserin, phentermine/topiramate, naltrexone SR/bupropion SR, antidiabetic drugs*

Introduction

Effective treatment of obesity continues to be a challenge for modern medicine. In Poland there are no specialised structures for comprehensive treatment of obesity, so diagnostics and treatment remain in the competence of family doctors and specialists. Unsettled epidemiological data clearly show that obesity has become a global problem in recent years and has reached the proportions of a global epidemic. Obesity is not only a medical problem as one of the risk factors for increasing morbidity and mortality in the general population, but also a socio-economic problem associated with the need to increase financial outlays for health. The prospective studies presented in numerous multicentre epidemiological studies predict that if the unfavourable trend toward increasing the prevalence of overweight and obesity in the global population is not hampered, the problem will gradually increase with all negative effects, for both the individual and the whole of society [1, 2].

Definition and classification

According to the American Medical Association, obesity was not officially classified as a separate disease unit until 2013, defined as the state in which the amount of energy delivered significantly outweighs its consumption by providing a positive energy balance [3]. Even a slight disproportion (< 0.5%) between energy delivered from food and consumption results in weight gain. On the other hand, the World Health Organisation (WHO), in a report from 2000, defines obesity as a chronic disease that, through abnormal or excessive accumulation of body fat, exacerbates "excessive weight that may impair health", thus requiring long-term strategies for effective prevention and management [2]. Simple, yet widely used in clinical practice, the ratio for overweight and obesity is the Queteleta II, also known as the Body Mass Index (BMI), which is the quotient of body mass expressed in kilograms per height squared expressed in square metres (BMI = [kg/m^2]) (Table I) [2].

The BMI does not directly assess body fat content, but studies show a significant correlation between BMI and other methods directly evaluating body fat, such as anthropometric measurements (skin thickness measurement), Bioelectrical Impedance Analysis (BIA), Total Body Electrical Conductivity (TOBEC), Dual Energy X-ray Absorptiometry (DEXA), hydrodensitometric method, or imaging (Computed Tomography, Magnetic Resonance). Another commonly used anthropometric examination evaluating the distribution of adipose tissue in the human body to determine the type of obesity (abdominal or perineal obesity) is the Waist Hip Ratio (WHR), the quotient of the waist circumference to the

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Table I. *WHO classification of Body Mass Index*

BMI [kg/m^2]	WHO classification
18.5–24.9	Normal weight
25.0–29.9	Overweight
30.0–34.9	Class 1 obesity
35.0–39.9	Class 2 obesity
40.0 and above	Class 3 obesity

Table II. *Obesity complications*

Obesity complications	
Mechanical	Osteoarthritis
	Sleep apnoea
	Hypoventilation syndrome
	Urinary incontinence
Metabolic	Insulin resistance, type 2 diabetes,
	Dyslipidaemia
	Cancer: breast, uterus, cervix, large intestine, oesophagus, pancreas, kidney, prostate
	Gout
	Non-alcoholic fatty liver
	Menstrual disorders
	Infertility
	Increased thyroid volume, moderate increase in TSH, T3, and ft3 concentrations
Circulatory	Hypertension
	Ischaemic heart disease
	Myocardial infarction
	Stroke
	Venous insufficiency, venous stasis
Other	Increased overall mortality
	Chronic inflammation and oxidative stress
	Dermatological disorders
	Low quality of life
	Mental illness (with depression dominance)

circumference of the hips expressed in centimetres (WHR = waist circumference [cm]/hip circumference [cm]). WHR values for men > 1.0 and WHR for women > 0.85 indicate an excess of lean and abdominal fat [2, 4–6]. Classification of BMI overweight and obesity has become a specific predictor in the risk assessment of complications related to overweight, which can be divided into four groups: mechanical, metabolic, circulatory, and other complications (Table II) [2, 7–11].

Epidemiology

The epidemiological data presented by the WHO in 2014 indicated that overweight and obesity in people over-18-years-old affects approximately 1.9 billion people, of which around 600 million are obese (13% of the total population). According to recent, current data it is estimated that throughout the world obesity occurs in 1 in 10 men and 1 in 7 women. In a large retrospective analysis from 2016 assessing the global trend of BMI in adults in 200 countries between 1975 and 2014, it was shown that obesity is already present in about 640 million people across the population, including 375 million women and 266 million men (in 1975 the number of obese people was about 105 million people, which indicates a six-fold increase over the past 40 years without a gender division). This percentage translates into a three-fold increase in the number of obese men, from 3.2% (1975) to 10.8% (2014), and among women over two-fold, from 6.4% (1975) to 14.9% (2014). In addition, it was found that global life-threatening obesity (BMI > 40 kg/m^2) can be diagnosed in about 1% of men and 2% of women (55 million adults). In the report, countries with the highest percentage of obese people are the United States and China. It is estimated that the United States still ranks first in terms of obesity, with 35% of men and 40% of women. According to the authors, if this unfavourable trend continues until 2025, the incidence of obesity among men will reach 18% and 21% among women, globally [1, 12]. On the other hand, a study presented by the World Food Security Index in 2016 draws attention to the epidemiological situation in the Gulf Cooperation Council States (Qatar, Kuwait, UAE, Bahrain, Saudi Arabia, Oman), which is serious, where drastic changes in eating habits have resulted in a significant increase in the number obese people (36.7%), which places this region of the world at the top of the prevalence of obese people before the United States (33.7%), Jordan (30.5%), and Turkey (29.5%) [13]. The WHO report of 2007 prepared for the European region showed that overweight may affect 30–80% of adults and 20% of children and adolescents, with one in three experiencing obesity. The incidence of obesity varies from 5.4% to 22.8% among men and from 7.1% to 35.6% among women [14]. Furthermore, in the above-mentioned World Food Security Index 2016, Poland was ranked fifth in Europe in terms of the highest proportion of obese people over the age of 20 years, behind Great Britain, the Czech Republic, Slovakia, and Ireland. This problem affects 25.2% of Polish society, and the average for Europe is 22.3% [13]. Similar epidemiological studies have also been conducted in Poland. In the NATPOL studies (Hypertension in Poland) evaluating the trend of changes in the prevalence and control of cardiovascular risk factors in Polish society, it has been shown that overweight and obesity affects approximately 53% of adult Polish people [15]. Similar conclusions are also drawn from

the presented preliminary analyses of the WOBASZ II study (Multi-Centre All-Polish Population Health Survey — II Edition), which was conducted at the turn of 2013–2014, and which is a continuation of the WOBASZ I study (2003–2005) evaluating the epidemiology of the prevalence and control of cardiovascular risk factors (CVD) in the population and monitoring of health behaviours and morbidity with respect to chronic social diseases. The study showed that the incidence of overweight and obesity has increased significantly in the male and female populations over the past 10 years. It has been shown that the obesity problem (BMI ≥ 30 kg/m^2) of people in their twenties plus (WOBASZ study) affects 26% of the country's population, affecting 25.9% of men and 26.1% of women, respectively. Comparing the preliminary results of the WOBASZ II study with the WOBASZ I study on obesity as one of the cardiovascular risk factors, there was a worrying increase detected in the prevalence of obesity by 3.9% in the general population over the past 10 years, at 5% in men and 3.4% in women, respectively [16–18].

Obesity treatment

The basis of treatment for obesity at every stage is behavioural therapy (diet and exercise adjusted to the health of the patient). Changing lifestyles is the most important element without which success will not be achieved, but permanent change in eating habits and a persistent increase in activity is not enough and motivation of patients to follow-up these changes is usually only periodic. Ineffective self-made lifestyle modifications often discourage patients from further efforts to reduce weight and often lead to behavioural health hazards (the use of "miracle" diets or unknowable sources of unknown activity). In the literature of the subject there is considerable evidence that intensive, specialised help (diet education, personal trainer, support groups) allows for better effects of behavioural treatment [19, 20]. Modern medicine is increasingly well-versed in promoting diet and physical activity through the use of pharmaceuticals and bariatric treatment. The choice of therapeutic treatment should depend on the patient's acceptance of the method chosen, co-morbidities, body mass index, goals, and needs (Tab. III) [21].

Despite the high efficacy and safety of bariatric surgeries [22–24], they are still not a frequently chosen therapeutic option by patients and physicians, especially because of the limited availability of bariatric surgery centres. Taking these facts into account, pharmacotherapy becomes an important aspect of obesity treatment. However, the availability and effectiveness of therapy cannot be the main predictors of treatment. The safety of patients during the therapy should be

Table III. *Selection of the therapeutic procedure depending on the BMI*

Treatment \ BMI	25.0–26.9	27.0–29.9	30.0–34.9	35.0–39.9	≥ 40
Behavioural	+ metabolic diseases	+	+	+	+
Pharmacological		+ metabolic diseases	+	+	+
Surgical				+ metabolic diseases	+

the base, as in the case of rimonabant and sibutramine, which was withdrawn from treatment [25]. Among the available pharmaceuticals are phentermine, orlistat, lorcaserin, phentermine with topiramate, naltrexone with slow release bupropion, and many antidiabetic medications. In spite of the availability of the aforementioned substances, further studies are underway on additional pharmaceuticals and combinations of already used drugs.

Phentermine

Phentermine is a substance that was approved by the FDA as early as in the second half of the twentieth century (1959) for the short-term treatment of obesity. This is a noradrenergic and probably dopaminergic sympathomimetic amine that increases the level of norepinephrine in the hypothalamus, enhancing the signal of the neoplastic proopiomelanocortin pathway for the release of α-MSH, which binds to the melanocortin 4 receptors, resulting in increased satiety and decreased appetite, but also increased energy expenditure. The recommended standard dose for adults given once daily is up to 37.5 mg before breakfast; however, individual dosing is allowed from 9.375 mg. The expected weight reduction is approximately 5% of baseline body weight, but in some cases this reduction can be as high as 10% [26]. In a meta-analysis of six studies in which the calculated average dose of phentermine was 27.5 mg/day and was administered for 13.2 weeks, 6.3 kg body weight loss was found [27]. Due to the increased risk of valvular heart disease, phentermine is contraindicated in patients with cardiovascular diseases.

In addition, this drug should not be used in co-occurring serious mental illness, pregnancy and breastfeeding, or addiction to psychoactive substances [28]. Therefore, the guidelines outlined by the European

Society of Endocrinology and Obesity Society of 2015 underline the lack of recommendations for the use of sympathomimetic agents, including phentramine, in patients with uncontrolled hypertension or with heart disease [21]. Most patients tolerate phentermine monotherapy well, and the most common side effects are dry mouth, sleep disorders, irritability, dizziness, and constipation. An additional advantage is the relatively low cost of therapy, but the lack of long-term treatment data and side effects currently excludes this drug from use in chronic therapy. Treatment of obese adolescents with phentermine seems to be also effective, but further studies are needed, particularly in terms of safety [29]. Phentermine preparations are not available in Poland; it is only possible to obtain them as part of a target import (Table IV).

Table IV. *Availability of drugs in the treatment of obesity in Poland and in the world*

Anti-obesity drug	FDA	EMA	Poland
Phentermine	Approved	Approved	Unavailable
Orlistat	Approved	Approved	Available
Lorcaserin	Approved	Unapproved	Unavailable
Phentermine/topiramate	Approved	Unapproved	Unavailable
Bupropion/naltrexone	Approved	Approved	Available
Liraglutide	Approved	Approved	Available — off-label obesity treatment

US Food and Drug Administration (FDA); European Medicines Agency (EMA)

Orlistat

This is a specific, long-acting gastric and pancreatic lipase inhibitor which by inactivating the active serine centre, deactivates these enzymes. This results in halting the triglyceride hydrolysis and reducing the absorption of fats from the gastrointestinal tract by approximately 30%. The recommended dosage is 120 mg in obese patients or 60 mg in overweight patients, repeated before, during, or immediately after major meals (for three days) [26]. In the meta-analysis studies, orlistat significantly reduced body weight (5–10% of baseline body weight) compared to placebo [30]. Better results can be achieved by combining orlistat with a low-calorie diet, and the treatment should be discontinued after 12 weeks unless weight loss is at least 5%. The four-year XENDOS study (Xenical for obesity prevention in obese patients) showed that after four years 52.8% of orlistat patients lost 5% of baseline weight, and 26.2% lost 10% of baseline weight. This study also showed a reduced progression from abnormal glucose tolerance (IGT) to overt type 2 diabetes (42% reduction in risk) [31]. During long-term treatment, this substance may reduce the absorption of fat-soluble vitamins (A, D, E, K), so supplementation with selected vitamin preparations is recommended [26]. In addition, gastrointestinal disorders, especially abdominal pain, bloating, fatty diarrhoea, rapid evacuation, and discoloration and dryness of the skin are observed during treatment. The use of orlistat may also be associated with the development of bleeding nodules, carotid stenosis, and varicose veins [32]. Due to its mechanism of action, orlistat appears to be the safest pharmacological option for treating obesity and has been registered in the European Union since 1999 and approved for long-term therapy, as reflected in the recommendations for treating obese cardiovascular disease patients (Tab. IV).

Lorcaserin

This selective serotonin 2C receptor agonist is approved for long-term treatment of obesity by the US Food and Drug Administration (FDA), but has not yet been approved by the European Medicines Agency (EMA) (Table IV). Its action selectively activates the 5HT-2c receptor on the anorexigenic POMC neurons located in the hypothalamus, resulting in a satiated feeling after consuming a less calorific meal [26]. The manufacturer's recommended dosage is one or two times daily in a dose of 10–20 mg, which should not be exceeded. The effectiveness of treatment is similar to orlistat or phentermine. The analysis of three randomised trials shows a loss of approximately 3.2 kg compared to placebo in the first year of therapy. Due to the small amount of side effects, lorcaserin therapy is rarely discontinued, so the expected end-effect of long-term treatment is usually positive [30]. The main side effects of treatment are headache, as well as dizziness, nausea, and upper respiratory tract infections. In patients with type 2 diabetes, the use of this substance has increased the risk of hypoglycaemia and often the need to reduce the dose of hypoglycaemic agents [33, 34]. Previously used drugs in this group such as fenfluramine and dexfenfluramine caused damage to the heart valves, which was the reason for their withdrawal from treatment [35]. However, lorcaserin, due to its selective effect on the 5-HT2C serotonin receptor (without stimulation of 5-HT2a and 5HT2b), does not show this type of side effect. Taking into account the mechanism of action, lorcaserin in combination with serotonergic or anti-dopaminergic drugs should be avoided because this can result in the development of serotonin syndrome or increased risk of valvulopathy. The ability to interact with the above-mentioned drugs does not disqualify lorcaserin in the treatment of obese patients

with cardiovascular disease [36]. In addition, patients treated with this substance reported improvements in carbohydrate metabolism, such as fasting glucose, insulin, and glycated haemoglobin, and improvement in lipid profile, but this effect was not maintained when lorcaserin was discontinued. In addition, there was a decrease in hsCRP and fibrinogen levels compared to placebo, as well as improved quality of life [33].

Phentermine/topiramate

Another drug for the treatment of obesity is a drug that combines low doses of phentermine and prolonged-release topiramate, which has been approved by the FDA, but remains without EMA approval (Tab. IV). The mode of action of phentermine and its anorectic effect is described above. Topiramate is an anticonvulsant that blocks the membrane-dependent sodium channels, increases GABA activity, and exhibits antagonism to glutamic acid receptors (AMPA/kainate receptors) and carbonic anhydrase [37, 38]. However, the exact mechanism of weight reduction is not fully understood. Animal studies suggest that topiramate increases energy expenditure and inhibits appetite, thereby reducing caloric intake [26, 36, 39]. Treatment with PHEN/TPM should be gradual. It is recommended that the initial dose be 3.75/23 mg once daily and then with good tolerance, after two weeks, it should be increased to 7.5/46 mg. If weight loss after three months of therapy is less than 3%, it is recommended that treatment be discontinued or increased to a dose of 15/92 mg. However, if weight loss is not achieved after the subsequent quarter, treatment should be discontinued [26, 36, 40]. It is also advisable to gradually reduce the dose (within 3–5 days) due to seizure episodes that might occur following sudden discontinuation of treatment by epilepsy patients [41, 42]. After this therapy, the expected weight reduction is between 5 and 10% of the weight. In the CONQUER study (double blind, placebo-controlled), significantly greater weight loss was observed in the phentermine/topiramate ER 7.5/46 mg and 15/92 mg group compared with placebo. High treatment efficacy (loss of ≥ 5% TBW in 70% of patients treated with the highest dose and 62% of standard dose, compared with 21% of placebo patients) was demonstrated [42]. Patient observation was continued in the 108-week SEQUEL study, which demonstrated the safety of cardiometabolic therapy and the beneficial effects of long-term therapy (weight loss > 20% starting at 15.3%/9.2%/2.2%) [41]. And here, the high efficiency of treatment compared with other preparations for obesity is worth mentioning [30]. In addition, blood pressure, triglyceride levels, and elevated HDL cholesterol were found during treatment. There was also a beneficial effect on the carbohydrate economy (decreased both fasting glucose and insulin, indicating improvement in insulin sensitivity), and in patients without recognised diabetes, it was associated with a decrease in progression to type 2 diabetes during the second year (54% reduction in progression to T2D in subjects receiving 7.5/46 mg and 76% reduction in 15/92 mg, compared with placebo) [41]. This formulation may also be used in obese depressed patients treated with selective serotonin reuptake inhibitors (SSRIs) or serotonin-norepinephrine reuptake inhibitors (SNRIs) [36]. It should be emphasised that the combination of phentermine and topiramate should not be used in pregnant women and those planning pregnancy, due to the teratogenicity of the latter [43]. A reasonable combination of low doses of the formulation minimises side effects while maintaining the effectiveness of weight loss at lower doses than monotherapy with particular ingredients, which is particularly important in obese patients with multiple loads [44]. However, this does not allow for the exclusion of side effects, including: paraesthesia, dizziness and headache, dry mouth, fatigue, and tachycardia [40, 43, 45]. The combination of phentermine and topiramide is expensive, although the components are relatively inexpensive, but the combination of substances in one dose provides a better chance of compliance. Considering the health consequences and costs of treating obesity complications, the use of this formulation may be particularly profitable in overweight and obese patients with two or more co-morbidities, if they remain on this treatment for a prolonged period of time, and the benefits remain after discontinuation of medication [46].

Naltrexone SR/bupropion SR

The naltroxone and bupropion-prolonged-acting drug is a central-active formulation used to assist weight loss during behavioural therapy. Naltrexone is an opioid receptor antagonist ($\mu > \kappa i > \delta$) that is used to treat alcohol and opioid dependence [47, 48]. Bupropion, used for more than 30 years as an antidepressant and to support the treatment of nicotine dependence, is a selective inhibitor of neuronal dopamine and noradrenaline reuptake (with minimal effect on indoleamine uptake) [49]. The neurochemical mechanisms exerted by the combination of naltrexone and bupropion, which regulate appetite suppression, are not well known. These substances affect the hypothalamic arch of the hypothalamus and the mesolimbic dopaminergic reward system. Bupropion alone (monotherapy) reduces weight [50]. In the hypothalamic arch of the hypothalamus, bupropion stimulates the neurons

expressing POMC to release α-MSH, which binds MC4-R and activates them similarly to phentermine. Simultaneously with the release of α-MSH, β-endorphin is released which, by binding to the μ receptor neurons on the POMC neurons, is the closing point of the negative feedback loop on the POMC neurons and leads to a decrease in α-MSH release. The addition of naltrexone, which alone does not cause weight loss, inhibits feedback, thus facilitating stronger and more prolonged activation of POMC neurons, amplifying continuous weight reduction and maintaining the outcome (Fig. 1) [51, 52]. Dosage should be gradually increased over a period of four weeks to a maximum of 32 mg naltrexone and 360 mg bupropion [26]. In a meta-study of four randomised clinical trials, weight loss was approximately 5 kg compared to placebo during one year of therapy, and a weight reduction of 10% or more was reported in one out of every three patients. The good tolerance and safety profile of this medicine are also worth mentioning. Phase 3 studies showed that the Number Needed to Treat (NNT) for participants who lost ≥ 5% body mass during the treatment with naltrexone SR/bupropion SR was four, and to lose ≥ 10% body mass the NNT was 6, while Number Needed to Harm (NNH) for the most common adverse effect, nausea, was 17 [53]. In addition, the observed side effects of the therapy were vomiting, headache and dizziness, and insomnia [36, 40]. Additional effects during treatment included decreased waist circumference, triglyceride levels with elevated HDL cholesterol levels, and reduction in insulin resistance [54]. Further evaluations are required to assess improvements in measures of cardiovascular and metabolic risk. Among the 8910 overweight or obese patients at increased cardiovascular risk, based on interstitial events performed after 25% of planned events, major adverse cardiovascular events (MACE) occurred in 59 placebo-treated patients (1.3%) and 35 naltrexone-bupropion-treated patients (0.8%; HR, 0.59; 95% CI, 0.39–0.90). After 50% of planned events, MACE occurred in 102 patients (2.3%) in the placebo group and in 90 patients (2.0%) in the naltrexone-bupropion group (HR, 0.88; adjusted 99.7% CI, 0.57–1.34), concluding that the study drug did not increase cardiovascular risk [55]. The treatment should be discontinued when significant increases in blood pressure and heart rate, and weight loss less than 5% within 3–4 months are observed [40]. Fujioka K et al. observed in a one-year follow-up that patients who achieved at least 5% reduction in early weight within the first 16 weeks were expected to maintain a clinically significant weight reduction in observation for more than one year [56]. Naltrexone/bupropion is more effective than orlistat and lorcaserin, but less than phentermine/topiramate [30]. This product has been approved by the FDA in 2014 and the EMA in 2015 and has been available in Poland since November 2016 (Table IV).

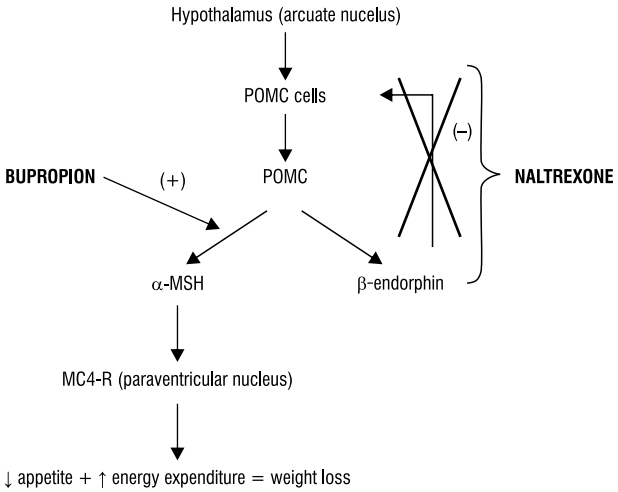

Figure 1. Mechanism of action of naltroxone and bupropion
POMC — *proopiomelanocortin, α-MSH — α-melanocyte stimiulating hormone, MC4-R — melanocortin 4 receptor*

Liraglutide 3.0

Liraglutide, a glucagon-like peptide-1 agonist (GLP-1), was originally registered in 2009 for the treatment of type 2 diabetes, and then in the treatment of obesity independently of diabetes. Its mechanism of action is glucose-dependent stimulation of insulin secretion from pancreatic β cells, inhibition of glucagon secretion by α cells in normoglycaemia, slowing of gastric emptying, and affecting the central nervous system causing appetite suppression [57, 58]. The recommended dosage for treating obesity is 0.6 mg with weekly increments of up to 3.0 mg once daily for subcutaneous injection. It is worth noting that the maximum recommended dose for the treatment of diabetes is 1.8 mg, but a dose of 3.0 mg /day results in better weight reduction with safer treatment [59]. Liraglutide is superior to lorcaserin, orlistat, or naltrexone/bupropion, resulting in weight loss in more than 5% of patients with BWT [30]. This drug is especially recommended in obese patients with type 2 diabetes [36] because it allows full-spectrum use, and a specific use should be found in patients with high cardiovascular risk because the LEADER trial showed that the use of liraglutide reduces cardiovascular deaths in patients with type 2 diabetes compared to placebo [60]. However, as demonstrated by the SCALE Diabetes and SCALE Obesity and Prediabetes studies, in both obese and non-diabetic patients, the therapeutic effects are significant compared to placebo (weight reduction of 5.9% in obese diabetics and 8.0% in obese and

overweight patients with no diabetes compared to about 2% reduction in placebo patients during 54 weeks) [61, 62]. In addition, the use of liraglutide in the treatment of obesity reduces the probability of developing type 2 diabetes and has a positive effect on blood pressure and lipid profile [62]. The most common side effects include nausea and diarrhoea, hypoglycaemia, constipation, vomiting, headache, indigestion, fatigue, dizziness, abdominal pain, and reversible elevations of lipase and amylase [40, 63].

Antidiabetic medications that reduce weight

Among the drugs used in the treatment of diabetes, there are also those that promote weight loss, but this effect, in a significant majority, brings a slimming effect only among diabetics. These drugs include metformin, SGLT2 inhibitors, GLP-1 agonists, and pramlintide.

Metformin is a first-line antihyperglycaemic drug in patients with type 2 diabetes. Many of the benefits of using it (high efficacy, no hypoglycaemic risk, low price), along with the most common side effects of gastrointestinal disorders that subside during treatment, as well as its use in the pre-diabetes states, make it a very common and often used preparation [26]. It has been proven that chronic therapy (2.8 years) of this biguanide derivative results in a reduction in basal body weight by approximately 2.5% [64], which is the result of a multifactor mechanism of action that is not fully understood [65]. This makes it possible to recommend metformin to any obese type 2 diabetic patient who has no contraindications for this substance [36].

Sodium glucose cotransporter 2 (SGLT-2) inhibitors, including but not limited to canagliflozin, dapagliflozin, and empagliflozin, reduce urinary glucose resorption, thus eliminating excess glucose from the blood and thereby eliminating unnecessary calories. The pharmacologically induced glycosuria results in weight loss, as well as diuretic effects and a hypotensive effect [66]. Estimated weight loss after at least 12 weeks of therapy is over 1.8 kg [67]. However, this effect must be accompanied by hyperglycaemia. In addition, the EMPA-REG OUTCOME trial demonstrated a reduction in mortality (both cardiovascular and total mortality) in empagliflozin-treated patients [68]. Therefore, given the overall spectrum of the effects of gliflozins, they should be used in obese patients with type 2 diabetes, who have a particularly high risk of cardiovascular events.

Another group of antidiabetic drugs that promote weight loss are **GLP-1 agonists**, such as exenatide, liraglutide, dulaglutide, and albigluide. Their mechanism of action has been described above, by the example of liraglutide. A comparative study of exenatide administered twice daily (10 μg) and long-acting exenatide 2 mg dosed once a week revealed similar weight reductions for both formulations (3.6 kg exenatide vs. 3.7 kg with LAR exenatide over a 30-week period) with better glycaemic control in patients taking long-acting mediation [69]. In addition, a 26-month LEAD-6 head-to-head comparison of liraglutide (1.8 mg daily) and exenatide (10 μg twice daily) demonstrated an advantage of using liraglutide for weight loss (3.24 kg vs. 2.87 kg) and hypoglycaemic action (HbA1C 1.12% vs. 0.79%) [70]. GLP-1 analogues should always be considered in obese diabetics, including those with high cardiovascular risk (especially liraglutide) [36, 60].

Pramlintide is a synthetic equivalent of amylin, which is secreted with insulin by pancreatic β cells in response to food intake. Its effect is to lower the postprandial glucose and glucagon levels and to slow down the emptying of the stomach. Pramlintide has been used in support of glycaemic control in patients with type 1 and type 2 diabetes since 2005 in the US [34, 71]. In a 16-week study, Aronne et al. demonstrated that pramlintide (applied up to a maximum dose of 240 micrograms daily) without lifestyle modification compared with placebo significantly reduced body weight and waist circumference. Weight loss of 5% and more was achieved in approximately 31% of the subjects (compared with 2% of the placebo, $p < 0.001$), as well as improved appetite control (72% vs. 31%) and weight control (63% vs. 24%) [72]. Further studies have shown that, with the use of the behavioural therapy and prolonged treatment with pramlintide, weight loss can reach more than 10% of baseline body weight, and the reduction effect is retained in the long term [73].

New therapeutic perceptions

The epidemic of obesity is forcing researchers to look for some new substances and new models of combinations of substances already known, which can be used safely and effectively to treat obesity. One of them is **Gelesis 100**, approved by the FDA, a hydrogel capsule (2.25 g twice daily) in which the molecules swell in the stomach and small intestine causing satiety and weight reduction. The Gelesis Loss Of Weight (GLOW) study evaluated the long-term safety and efficacy of Gelesis 100 in obese patients or obese patients with diagnosed pre-diabetes and type 2 diabetes, with a non-significant risk. However, extensive research is still underway [74].

Cetilistat, like orlistat, inhibits pancreatic lipase activity. In a 12-week study, a weight reduction of 3.3–4.1 kg was observed in patients treated with cetilistat compared to placebo [75, 76].

Research on new combinations of drugs has also been initiated because their different mechanisms of action allow the combination of two or more classes of substances, opening numerous therapeutic pathways that might be used to treat obesity. One of them is a combination of **bupropion** and **zonisamide** (antiepileptic), which during a 12-week randomized study in 18 obese patients showed a 7.2 kg weight reduction compared to 2.9 kg in zonisamide monotherapy [77].

The combination of **pramlintide** with **phentermine** was demonstrated in which a weight reduction of 11.3% was shown in a 24-week study, which was statistically more effective compared to placebo and pramlintide alone [78].

Results of the DURATION-8 study, including weight reduction with **dapagliflozin** (10 mg once a day) and **exenatide** (2 mg once weekly) in patients with type 2 diabetes mismatched with metformin (1.5 g/day), are promising. They both confirm the utility of these glycaemic control drugs and obesity therapy (weight reduction 3.4 kg at 28 weeks) [79]. Double combined therapy with these substances has also been shown to be effective in obese non-diabetic patients, both in terms of weight reduction, prediabetes, and beneficial effects on blood pressure [80].

In the last year the data on the combination of inhibitor SGLT2 (**canagliflozin**) with **phentermine** have also been published, with 6.9% weight reduction compared with placebo (26 weeks) in overweight and obese diabetic patients [81].

Treatment with these substances as well as drug combinations requires, however, further research, especially concerning the safety of long-term therapy.

Conclusions

Obesity is a major health problem in the world, which results in numerous diseases, especially cardiovascular and metabolic. Complications of obesity generate huge costs, and although pharmacological treatment is often expensive, it is still profitable for individuals and the entire health system. The use of modern pharmacotherapy allows one to expect a reduction of 5–10% of body weight. When considering each patient's clinical presentation, the knowledge of each drug's mechanism of action, efficacy, and side-effect profile can help in selecting an anti-obesity medication for his or her weight loss efforts. Therefore, emphasis should be placed on the individualisation of pharmacotherapy, without forgetting the necessary basis for achieving a lasting effect, such as a long-term change in eating habits and a lasting increase in activity. Although behavioural therapy and pharmacotherapy can be effective, many obese patients are dissatisfied and the results are short-lived, so there is still a need for some new substances and drug combinations. In case of ineffective treatment, the next step should be bariatric treatment.

Conflict of interest

The authors declare no conflict of interest. No honorarium, grant, or other form of payment was given to anyone to produce the manuscript.

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