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Available Pharmacological Methods of Obesity Treatment Worldwide - Drugs Review

Weronika Zielińska
Medical University of Lublin
Aleje Racławickie 1, 20-059 Lublin
w09290929@gmail.com
ORCID: 0009-0007-0707-9590

Joanna Wanat
Medical University of Lublin
Aleje Racławickie 1, 20-059 Lublin
asiawanat2000@gmail.com
ORCID: 0009-0009-3349-3618

Izabela Dzikowska
Medical University of Lublin
Aleje Racławickie 1, 20-059 Lublin
dzikowskaizabela2@gmail.com
ORCID: 0009-0006-5539-3771

Agata Siejka
Medical University of Lublin
Aleje Racławickie 1, 20-059 Lublin
agata.siejka12@gmail.com
ORCID: 0009-0009-2332-0115

Daria Stefaniak
Medical University of Lublin
Aleje Racławickie 1, 20-059 Lublin
dariastefaniak18@gmail.com
ORCID: 0009-0002-2207-4177

Aleksandra Warunek
Medical University of Lublin
Aleje Racławickie 1, 20-059 Lublin
condition.aleks@gmail.com
ORCID: 0009-0000-7542-6522

Gabriela Gronowicz
Medical University of Lublin
Aleje Racławickie 1, 20-059 Lublin
gabagronowicz@gmail.com
ORCID: 0009-0009-4034-1284

Wojciech Homa
Wojewódzki Szpital Specjalistyczny
al. Kraśnicka 100, 20-718 Lublin
wojciech.homa2@gmail.com
ORCID: 0000-0003-2177-8818

Michał Chról
Medical University of Lublin
Aleje Racławickie 1, 20-059 Lublin
michuGBE@gmail.com
ORCID: 0009-0005-7776-6260

ABSTRACT:

Introduction and Purpose: The prevalence of obesity is increasing year by year all over the world. Along with the progression of the disease, there is also progress in the pharmacotherapy of obesity. The developing epidemic of obesity indicates that non-pharmacological methods are not able to solve this problem. For over 60 years, there has been a search for the ideal drug that would allow not only weight loss but also maintaining a lower bodyweight and reducing the cardiovascular risk that obesity carries. It is very important to thoroughly examine the intricacies and impact of the drugs used in order to properly select the drug for each case individually, depending on the source of obesity. The aim of this review is to present the available drugs together with the mechanism of their actions and the side effects associated with their use.

Brief Description of the State of Knowledge: There are currently 7 drugs approved by the Food and Drug Administration (FDA) and 6 approved by the European Medicines Agency (EMA) for long-term (over 12 weeks) treatment of obesity. All available drugs are prescribed for patients with a body mass index of≥ 30 kg/m2 or ≥ 27 kg/m2 with concomitant comorbidity. However, their use should be combined with intervention in the lifestyle of the patients.

Summary: Obesity affects a large part of society and the number of patients is still growing. This global problem is a therapeutic challenge for doctors. A properly selected drug for the patient's needs may prove to be crucial in the treatment of obesity.

Materials and Methods: The literature review was conducted using the Google Scholar database

Keywords: obesity; obesity treatment; FDA; EMA; drugs mechanism; side effects

INTRODUCTION:

Obesity is a multifactorial disease in which the body mass index (BMI)≥ 30kg/m2. This is one of the major health problems of today. Based on current data from the World Health Organization (WHO), more than a billion people worldwide struggle with obesity, of which about 650 million are adults. This number is still growing. In the past, this problem mainly affected developed countries [1,2,18,19,21]. This disorder is associated with environmental and genetic factors. High-calorie food and a sedentary lifestyle results in significantly reduced energy expenditure. Currently, obesity is also a growing problem in developing countries. Obesity is a chronic disease associated with the occurrence of excessive adipose tissue. Patients with obesity are much more susceptible to diseases such as type 2 diabetes, fatty liver disease associated with metabolic disorders, cardiovascular diseases, degenerative joint disease or sleep apnea [1,2,18,19,21]

There are various methods of treating obesity, such as lifestyle changes, pharmacotherapy, and bariatric surgery. The basic form of treatment is lifestyle modification, which involves balanced nutrition, physical activity, and changing the daily habits of patients. The above behaviors allow you to reduce body weight and reduce high cardiometabolic risk. However, lifestyle modification alone may not be sufficient to maintain a healthy body weight in the long term. From one third to two thirds of the lost body weight returns within a year of completing therapy, while even over 95% of the lost body weight returns within 5 years of completing therapy [3]. Organizations such as The Obesity Society, The Endocrine Society, and the American Association of Clinical Endocrinologists recommend pharmacological treatment for patients with a BMI of ≥ 30 kg/m2 or a BMI of ≥ 27 kg/m2 with additional comorbidities [3].

Treatment by changing lifestyle.

This treatment aims to reduce calorie intake while increasing energy expenditure, thereby maintaining a negative energy balance.

Psychosocial factors such as stress and mental health should also be taken into account when treating obesity. They can be crucial when modifying patients' habits[4].

Clinically significant weight loss is a loss of 5% of body weight from baseline with improvement in cardiovascular risk factors[5]. In patients who do not achieve an appropriate body weight through lifestyle modification, pharmacotherapy is strongly recommended. Energy intake is largely controlled by hormonal pathways. Current pharmacotherapy for obesity is directed at the neurohormonal abnormalities that cause weight gain and prevent sustained weight loss[3]. Development of antiobesity drugs is focused not only on weight loss but also on their impact on cardiovascular risk. The goals of these drugs are primary, secondary, and tertiary prevention. The greatest benefits are achieved when pharmacotherapy is combined with lifestyle modification. There are currently nine different drugs approved by the FDA for the treatment of obesity[3].

Phentermine

It is one of the first drugs approved for use in the pharmacotherapy of obesity. This drug was approved in 1959 for short-term use, i.e. for a period of less than 12 weeks[6]. Phentermine has sympathomimetic, anorexigenic effects, belongs to the amine group and is a derivative of amphetamine. Its action is based on the stimulation of the satiety center by upregulating such neurotransmitters as dopamine, noradrenaline, serotonin.

Phentermine may contribute to increased blood pressure and heart rate[6].

Diethylpropion

This is another drug used only for a period of no longer than 12 weeks. Like phentermine, diethylpropion has a strong anorectic effect. The mechanism of action of diethylpropion also involves the intensification of the release of catecholamines such as noradrenaline or dopamine in the central nervous system[7,8]. It is a derivative of amphetamine. When using this substance, side effects such as pulmonary hypertension, valvular damage, and myocardial fibrosis are possible (these may apply to all amphetamine derivatives). Diethylpropion and phentermine may cause addiction and lead to overdose[7,8].

Orlistat

Orlistat is a drug approved for long-term use in both adults and adolescents. The mechanism of action of this drug is to inhibit gastrointestinal and pancreatic lipases, which reduces the absorption of fats from the gastrointestinal tract. This blocks the absorption of about one third of fatty acids that are supplied with food. Due to the mechanism of action, this drug will be more effective in people who eat foods high in fat. This drug does not affect appetite, only reduces the absorption of calories[5,3,23]. Orlistat supports weight loss and weight maintenance, and additionally improves insulin sensitivity and lowers blood glucose levels. The side effects of using this substance sometimes cause discontinuation of therapy. These include fatty stools, increased urge to defecate, fatty spotting, fecal incontinence. It is recommended to use fiber together with orlistat. This drug may cause easy-to-correct deficiencies of fat-soluble vitamins[5,3,23]. Orlistat was approved for the treatment of obesity by the European Medicines Agency (EMA) in 1998 and by the Food and Drug Administration (FDA) in 1999 [9].

Phentermina-Topiramate

Topiramate reduces neuronal excitation and increases neuronal inhibition. It blocks sodium channels and increases GABA concentration in the brain. Additionally, it has an antagonist effect on AMPA and KAR receptors and is an inhibitor of carbonic anhydrase[10]. The probable effects of topiramate on weight loss include reduced calorie intake, increased body fat, cholesterol and triglyceride levels. Studies indicate that topiramate stimulates lipoprotein lipase present in brown adipose tissue and skeletal muscle. Another possible effect of topiramate is its effect on the leptin pathway, a hormone involved in fat storage[10].

Topiramate is approved for the treatment of epilepsy and the prevention of migraines. In combination with the above-described phentermine, it creates a drug used for the long-term treatment of obesity. It is used in obese adults with a BMI ≥ 30 kg/m2 or a BMI ≥ 27 kg/m2 with at least one comorbidity and in children aged twelve years and older with a BMI of ≥ 95.This drug consists of immediate-release phentermine and extended-release topiramate[11]. It was approved for the treatment of obesity by the Food and Drug Administration (FDA) in 2012. The European Medicines Agency (EMA) has not approved the combination of phentermine and topiramate for the treatment of patients with obesity[9].

The drug is contraindicated in patients with cardiovascular diseases, pregnancy, hyperparathyroidism, glaucoma and in people taking MAO inhibitors within 14 days.

Adverse effects of the drug include paresthesia, dizziness, dry mouth, constipation, taste disturbances, insomnia, and anxiety. Discontinuation of the drug should be done gradually, because rapid discontinuation of topiramate may cause seizures [5,3].

Bupropion-naltrexone

This is a combination of two drugs with different mechanisms of action. This combination is approved for long-term treatment of obesity. The first component of the drug, bupropion, is used in the treatment of depression. Its mechanism of action is the inhibition of the reuptake of noradrenaline and dopamine. Bupropion has also been used in the pharmacotherapy of nicotine addiction. Naltrexone is an opioid antagonist, has high affinity for the receptorμ-opioid. It is used in the treatment of alcohol and opioid addiction. The above drugs also show synergistic effects In the hypothalamic melanocortin system and in the hypothalamic reward system [12]. Part of the hypothalamus is the arcuate nucleus, which contains proopiomelanocortin (POMC) cells. POMC cells produce melanocyte-stimulating hormone (alpha-MSH), beta-endorphin and endogenous opioid. Reduced need for food intake, increased energy expenditure and weight loss are the effects of alpha-MSH activating the melanocortin-4 receptor (MC4R). The activity of POMC cells is reduced by beta-endorphin, which binds to the inhibitory opioid receptor μ (MOP-R). Bupropion, which is a weak dopamine and norepinephrine reuptake inhibitor, increases POMC cell production and alpha-MSH and beta-endorphin release in vitro. Naltrexone blocks MOP-R, so the beta-endorphin inhibitory feedback loop in POMC cells is disrupted. The combination of the above drugs significantly enhances POMC signaling, more than either drug alone [12].

This combination of drugs should not be used in patients with uncontrolled hypertension, bulimia and anorexia nervosa. Adverse reactions that may occur during the use of the drug include nausea, vomiting, constipation, dry mouth, and insomnia [5].

The drug was approved for the treatment of obesity in 2014 by the FDA and in 2015 by the EMA[9].

Liraglutide

Liraglutide is a short-acting glucagon-like peptide (GLP-1) agonist. It is an analogue of human GLP-1 and its amino acid sequence has 97% identity with the amino acid sequence of human endogenous GLP-1. Liraglutide is a drug originally approved for the treatment of type 2 diabetes. GLP-1 is an incretin hormone secreted after meals [13,3]. Liraglutide binds to

pancreatic receptors, therefore its function is to inhibit glucagon secretion and increase insulin secretion in a glucose-dependent manner. During hyperglycemia, GLP-1 receptors are activated in the pancreatic islets and insulin secretion is increased with simultaneous inhibition of glucagon secretion. In hypoglycemia, glucagon secretion remains unchanged, while insulin secretion is reduced [13,3]. Additionally, liraglutide inhibits gastric emptying, responsible for causing a feeling of satiety after meals, which leads to a decrease in appetite and the amount of food consumed. GLP-1 receptors are also found in the central nervous system and the digestive tract. When they are stimulated, appetite decreases in response and glucose is absorbed more slowly because stomach emptying is slowed down. The main side effects are gastrointestinal symptoms and a slight increase in heart rate. Before starting liraglutide, women of childbearing age should perform a pregnancy test [13,3]. This drug was approved for the treatment of obesity in 2014 by the FDA and in 2015 by the EMA [9].

Setmelanotide

Setmelanotide is an octa-acid cyclic peptide, a selective agonist of the melanocortin 4 receptor. The drug was originally approved for the treatment of monogenic or syndromic obesity in both adults and children older than 6 years[14]. Patients were started on the drug because of defects affecting the melanocortin 4 pathway, with deficiency of promyelancortin, convertase protein 1, and leptin receptor. Setmelanotide was subsequently approved for use in Bardet-Biedl syndrome. Studies are ongoing on the use of setmelanotide in diseases such as Prader-Willi syndrome, Alstrom, hypothalamic obesity[14].

Setmelanotide affects the paraventricular nucleus of the hypothalamus and the lateral part of the hypothalamus. The mechanism of action of the drug is based on binding to the melanocortin 4 receptor and replacing the missing link in the hypothalamic leptin/melanocortin pathway. This results in reduced appetite and improved insulin resistance. Setmelanotide also affects other melanocortin receptors responsible for regulating immune functions, pigmentation, sebaceous gland activity or adrenal function. This drug additionally induces the activation of the nuclear factor of activated T cells (NFAT). NFAT proteins have been detected in adipocytes, whose signaling is probably impaired in patients with obesity. The most common adverse effects of setmelanotide are skin hyperpigmentation and other reactions at the injection site, because this drug is administered as a subcutaneous injection. Other reported adverse effects include headache, dry mouth, nausea, vomiting, and diarrhea [14].

Setmelanotide was approved for use in the pharmacotherapy of obesity in 2020 by the FDA and in 2021 by the EMA [9].

Semaglutide

Semaglutide is a potent, long-acting analogue of glucagon-like peptide 1 (GLP-1). This drug can be administered once a week, unlike the above-described liraglutide, which must be administered daily. Its single, weekly dose is 2.4 mg. Semaglutide was originally approved for the treatment of type 2 diabetes. The functions of this drug are to reduce calorie intake, reduce the feeling of hunger and increase the feeling of fullness. Studies have shown that semaglutide helps regulate diet by reducing the need to eat fatty and high-calorie foods. Additionally, this drug delays fat and glucose metabolism and gastric emptying time[3,5,15,20]. Semaglutide is intended to reduce the risk of cardiovascular complications in overweight and obese people and maintain long-term reduced body weight. The side effects of the drug are typical gastrointestinal symptoms such as nausea, vomiting, diarrhea.

Semaglutide is contraindicated in patients with a personal or family history of medullary thyroid cancer and multiple endocrine neoplasia type 2 syndrome [3,5,15,20]. The drug was approved for use in obese patients by the EMA and FDA in 2021[9].

Tirzepatid

It is the first dual agonist approved for the treatment of obesity. Tirzepatide is an agonist of the glucagon-like-1 (GLP-1) receptor and glucose-dependent insulinotropic peptide (GIP). The original use of this drug is type 2 diabetes. Tirzepatide is a comparable GIP receptor agonist to naturally occurring GIP in the body, while its affinity for the GLP-1 receptor is about five times lower than the native hormone. GIP is a hormone secreted by K cells located in the duodenum and jejunum. Its functions are to stimulate insulin secretion and to stimulate glucagon in non-diabetic type 2 patients. GIP also increases energy storage and improves insulin sensitivity in adipose tissue[16,24].

The hormone GLP-1 is released from L cells present in the ileum and colon. Its functions include slowing gastric emptying, increasing the feeling of satiety and consequently reducing food intake. GLP1 also stimulates insulin secretion and decreases glucagon secretion [16]. The use of tirzepatide in the treatment of obesity has been analyzed in 4 clinical trials SURMOUNT 1-4[16,17,22].

Clinical studies indicate that tirzepatide reduces food intake and appetite, because it increases the feeling of satiety and simultaneously reduces hunger. This drug also increases lipid oxidation. Tirzepatide additionally stabilizes glycemia and improves its control, because it lowers fasting and postprandial glycemia in people with type 2 diabetes. The mechanisms enabling these functions are the improvement of beta cell function and increased insulin sensitivity, while reducing glucagon levels and significantly delaying gastric emptying. Clinical studies also indicate that tirzepatide reduces complications of obesity such as steatohepatitis associated with metabolic disorders and mortality in patients with obstructive sleep apnea.
The main side effects of the drug are gastrointestinal symptoms, but the discontinuation of treatment due to these symptoms was low in the studies conducted. Tirzepatide affects the absorption of oral contraceptives that contain estradiol and may reduce their effectiveness [16,17,22]. The drug was approved for the treatment of obesity in 2023 by the EMA and FDA [9].

Summary: The reviewed papers and articles provide valuable information on how obesity pharmacotherapy has developed over the years and that it is worth continuing to search for new drugs that offer the least side effects. A thorough understanding of the mechanism of obesity and its complications allows for matching the right drug directly to the patient's needs. It is equally important to thoroughly examine all the mechanisms of approved drugs and those that have good prognosis.
Conclusions: This review examines the available treatments for obesity, focusing primarily on pharmacotherapy. Further research into the mechanism of action of drugs is needed to develop new options for dealing with the obesity epidemic. Understanding the concept of obesity and how to combat it may be crucial in developing new strategies not only for treating but also preventing obesity. Further research should focus on developing optimal drug doses and drug combinations that could maximize the effectiveness of therapy.

Disclosure:

Author's contribution:
Conceptualization: Weronika Zielińska
Methodology: Weronika Zielińska, Daria Stefaniak, Michał Chról

Formal analysis: Aleksandra Warunek, Izabela Dzikowska, Wojciech Homa, Joanna Wanat, Agata Siejka

Investigation: Weronika Zielińska, Gabriela Gronowicz, Daria Stefaniak, Michał Chról, Joanna Wanat

Data curation: Aleksandra Warunek, Wojciech Homa, Joanna Wanat, Gabriela Gronowicz

Writing- original draft preparation: Weronika Zielińska, Izabela Dzikowska, Agata Siejka, Michał Chról

Writing- review and editing: Weronika Zielińska, Daria Stefaniak, Aleksandra Warunek, Gabriela Gronowicz

Supervision: Agata Siejka, Izabela Dzikowska

Project Administration: Weronika Zielińska, Joanna Wanat

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