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Pharmacotherapy of obesity: *state of the art and perspectives*

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Abstract

Obesity is a chronic, progressive, and recurring disease. The prevalence of obesity has reached pandemic proportions, along with overweight-related conditions like diabetes, cardiovascular diseases, and certain cancers. Reducing residual morbidity is the main goal of obesity treatment. Pharmacotherapy is intended for patients who have not responded to lifestyle interventions. There are currently six anti-obesity medications (orlistat, phentermine/topiramate, naltrexone/bupropion, liraglutide, semaglutide, and tirzepatide) approved for long-term obesity management. Most of them, except orlistat, predominantly act centrally by increasing satiety, as well as reducing appetite and food reward. The most effective anti-obesity drugs are semaglutide and tirzepatide, which might provide weight loss of more than 10% of the initial weight. Although all anti-obesity medications have been demonstrated to improve cardiometabolic risk factors, only liraglutide and semaglutide lower the risk of major cardiovascular events in patients with or without established cardiovascular disease. A personalized approach, considering both drug (weight-reducing capacity and drug safety) and patient (comorbidities, age, and the patient's preferences) features, guarantees the best results. In this article, we will critically appraise the efficacy and safety of currently approved anti-obesity medications and those in the pipeline.

Key words: liraglutide, semaglutide, tirzepatide, personalized approach

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Introduction

Obesity is a major threat to public health due to its high prevalence, associated complications, and increased risk of all-cause mortality. Overweight and obesity are well-known risk factors for insulin resistance, type 2 diabetes, hypertension, dyslipidemia, cardiovascular diseases, osteoarthritis, and certain cancers (breast, colon, gallbladder, pancreas, and kidney) (1, 2). In addition, obesity contributes to the poor clinical outcomes of many diseases. There is compelling evidence that obesity therapy can delay the progression of prediabetes to type 2 diabetes (3, 4) and improve glycemic control in people diagnosed with type 2 diabetes (5). Therefore, weight control is the principal measure in the prevention of many chronic noncommunicable diseases and in improving their management, if they occur.

The prevalence of obesity has reached pandemic levels, as have overweight-related comorbidities. Between 1990 and 2022, the percentage of children and adolescents (5–19 years) living with obesity increased fourfold (2% to 8%), and that of adults (above 18 years) more than doubled (7% to 16%). The most recent data for 2022 evidenced that 2.5 billion adults were overweight. Of these, about 890 million have been diagnosed with obesity (6, 7). It is interesting to observe that women are more likely than men to be obese. Certain sex-specific traits are also present in obesity-related comorbidities, such as osteoarthritis and type 2 diabetes (8). A gender-driven approach might be needed to improve obesity/obesity-related comorbidity management.

Obesity is a chronic, progressive, and recurring disease. It was suggested that obesity should be considered a chronic disease, with people with obesity no longer being stigmatized as having a “weak character” (9). An argument for this statement is the fact that distinct pathophysiologic mechanisms lead to excess fat accumulation, combined with homeostatic mechanisms that impede weight loss and contribute to further weight gain. The duration of exposure to obesity is also important. If it has started early in life, a person is prone to developing multiple obesity-related complications. With 14,502 participants diagnosed with obesity in the ACTION-IO trial, it was shown that the majority of them recognized their health problem as an illness but chose not to seek medical attention (10), making obesity a huge health threat.

Obesity is a complex and multifactorial disorder. Common risk factors for obesity include easy access to energy-dense foods and reduced physical activity, i.e., an unhealthy lifestyle. Sleep deprivation, circadian dysrhythmia, chronic stress, and the use of certain medications (e.g., antipsychotic drugs, mirtazapine, and valproate) are positive risk modifiers. The estimated heritability of obesity is 40–70% (11), which is comparable to the genetic basis of heart disease (34–53%) (12) or breast cancer (25–56%) (13). Thus, the complex interplay of genetic and environmental factors contributes to the rise of obesity.

Individuals with obesity have a higher risk of functional disability and overall mortality than people living with a normal body weight. Therefore, obesity is linked to a

life expectancy shortened by 5 to 20 years, depending on the severity of excess weight, the length of time it has been present, and the appearance of related comorbidities (14).

The economic impact of obesity is high, including both direct and indirect healthcare costs. It seems a bit awkward that health insurance covers costs due to obesity-associated complications but rarely obesity management itself. Given that even a small weight loss of 3–5% results in clinically significant health benefits (15), prompt and rational management of obesity could minimize medical expenses associated with treating obesity-related complications. More proactive management of obesity is mandatory for all health professionals.

In this article, we aim to summarize the current and future pharmacological approaches to obesity management and provide the tools for its rational use in the pharmaceutical practice.

Regulation of body weight

An overview of body weight regulation will be made in order to discuss the mode of action of approved and future anti-obesity medications and to increase awareness of the expected risk of weight regain after medication withdrawal.

The body's energy storage is determined by the balance of energy intake and expenditure. Because excess energy is primarily stored as body fat, whether the body fat (i.e., body weight) will be gained or lost depends on the balance of energy intake and expenditure. The maintenance of a normal body weight is highly dependent on hunger/satiety signals. A sophisticated neuroendocrine system, relying on bidirectional crosstalk between the brain and the periphery (gut and adipose tissue), regulates hunger and satiety.

The central nervous pathways involved in the homeostasis of food intake mainly originate from the *arcuate nucleus* of the hypothalamus. There are two key competing mechanisms that influence food intake and energy expenditure: the **orexigenic pathway** that secretes *neuropeptide Y* (NPY) and *agouti-related peptide* (AgRP), whose activation increases food intake and decreases energy expenditure; and the **anorexigenic pathway** that secretes *pro-opiomelanocortin* (POMC) and *cocaine- and amphetamine-regulated transcript* (CART) peptide, which reduces food intake and increases energy expenditure. These pathways and certain loci of the brainstem receive afferent signals from the periphery through afferent fibers of the vagus nerve that project to the *nucleus tractus solitarius* (NTS), or *via* the circulation, which trigger efferent neuro-hormonal feedback (Figure 1). Brain regions close to the brainstem and hypothalamus, as well as dopaminergic brain reward centers in the mesolimbic pathway, have all been linked to hedonistic eating behavior (14, 16).

Peripheral signaling involved in food-intake regulation is even more complex. Many orexigenic and anorexigenic hormones, secreted by the gut, the liver, the pancreas, and the adipose tissues, are capable of modulating appetite and satiety. Some of them are *short-term regulators* of food intake that are either secreted in anticipation of (ghrelin),

response to (cholecystokinin (CCK), glucagon-like peptide 1 (GLP-1), glucose-dependent insulinotropic polypeptide (GIP)) or deprivation from (glucagon) nutrients. There are also *long-term regulators* of food intake released at the periphery, such as leptin, insulin, and amylin. The origin and specific role of peripheral hormones are as follows (14, 16, 17) (Figure 1):

- **Ghrelin**, an *orexigenic hormone*, is released from enteroendocrine cells in response to food consumption. By activating NPY/AgPR neurons, as well as dopaminergic neurons in the ventral tegmentum area, it promotes homeostatic food intake.
- **CCK,** an *anorexigenic hormone,* is released from intestinal cells in response to nutrient ingestion. Through vagal afferents, CCK sends satiety inputs to the brainstem, which it then projects to the hypothalamus. As a result, less food is consumed.
- **GLP-1,** an *anorexigenic hormone,* is secreted by enteroendocrine cells in response to nutrient ingestion, but there is also a centrally originated hormone. It decreases food intake *via* CNS mechanisms that seem to involve direct activation of POMC/CART neurons, but also activation of neurons in the area postrema and NTS. GLP-1 also modulates hedonic food intake by acting on the dopaminergic brain reward system.
- **GIP** is released by K cells in the small intestine in reaction to meal consumption. Its role in the energy metabolism is still unclear because both GIP-receptor activation and blockade have been linked to weight loss.
- **Glucagon**, an *anorexigenic hormone*, is secreted by the pancreatic alpha-cells. It reduces body weight by a variety of mechanisms, such as promoting energy expenditure and lipolysis while reducing appetite.
- **Leptin**, an *anorexigenic hormone*, is secreted mainly by adipocytes. Leptin binds to its receptors on POMC-producing neurons, which leads to reduced food intake.
- **Insulin**, an *anorexigenic hormone*, secreted by the pancreatic beta-cells, is known to decrease food intake *via* centrally-mediated mechanisms.
- **Amylin**, an *anorexigenic hormone*, is co-secreted with insulin, which also decreases homeostatic food intake but affects hedonic eating behaviour *via* signaling through the mesolimbic dopamine system as well.

In addition to the homeostatic control of food intake, *environmental factors* like food odor and palatability, as well as *personal lifestyle* choices like taste preferences, social habits, and circadian rhythm, affect hunger and satiety.

There is a substantial risk of weight regain after stopping anti-obesity medications. When weight loss occurs, especially in a fast manner, persistent hunger and appetite increase, in line with the “hypothalamic set-point theory”. Reduced leptin levels cause increased appetite and reduced thermogenesis, which is at least partially responsible for this

effect. Because adipocytes shrink in size but not in quantity during weight reduction, modifications to the biology of adipose tissue also play a role in weight gain. An imbalance in neural regulatory signaling might occur upon weight loss, meaning the predominance of reward-related signaling, which encourages a high-calorie food intake (18).

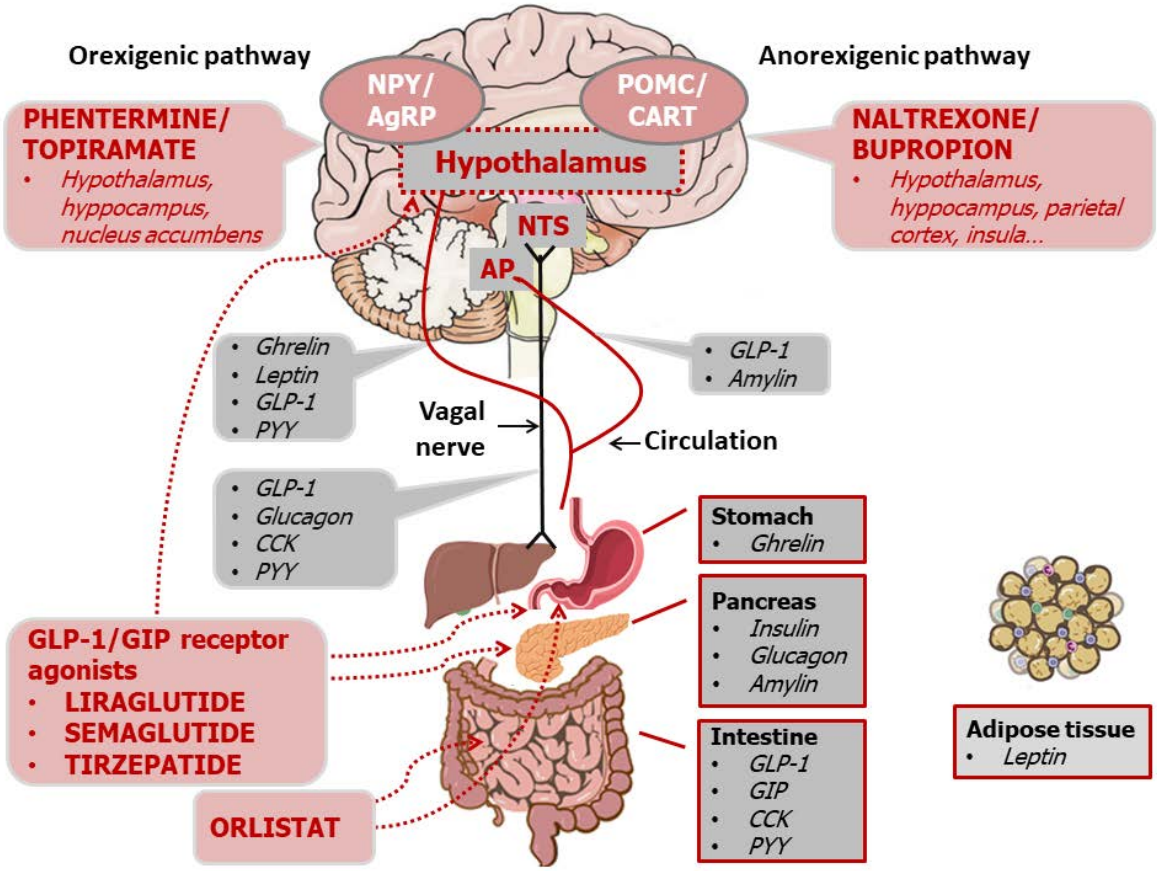

Figure 1. Neuronal-hormonal regulation of food intake with the site(s) of action of approved anti-obesity medications (*prepared according to References no 1 and 14*).

AgPR, agouti-related peptide; AP, area postrema; CART, cocaine- and amphetamine-regulated transcript; CCK, cholecystokinin; GIP, glucose-dependent insulinotropic peptide; GLP-1, glucagon-like peptide; NPY, neuropeptide Y; NTS, nucleus tractus solitarius; PYY, peptide tyrosine tyrosine; POMC, pro-opiomelanocortin.

Slika 1. Nervna i hormonska regulacija unosa hrane sa mestima dejstva odobrenih lekova za lečenje gojaznosti (*pripremljeno prema Referencama br. 1 i 14*).

AgPR, aguti-srodan peptid; AP, area postrema; CART, kokainom- i amfetaminom-regulisani transkript; CCK, holecistokinin; GIP, glukoza-zavisni insulinotropni peptid; GLP-1, glukagonu-sličan peptid; NPY, neuropeptid Y; NTS, nucleus tractus solitarius; PYY, peptid tirozin tirozin; POMC, pro-opiomelanokortin.

Therapy of obesity

Overweight and obesity are defined as excessive or abnormal fat accumulation that represents a significant health risk. A commonly accepted parameter to quantify levels of deviation from normal body weight is the body mass index (BMI). It is calculated by dividing an individual's weight in kilograms by their height in meters squared. If BMI is over 25 kg/m^2, the person is considered *overweight*, and a BMI higher than 30 kg/m^2 indicates a *person with obesity* (6). As it was stated before, a higher BMI is linked to an increased risk of diabetes, cardiovascular disease, and death from any cause. It also negatively impacts quality-of-life outcomes. As a result, BMI serves as a benchmark for when and how to start anti-obesity therapy.

The **primary goals** of weight management are to reduce body weight and maintain a normal body weight. No less important is the **secondary goal**, which is to reduce the overweight-associated health risk, especially for diabetes and cardiovascular disease development. Treatment goals and the treatment strategy should be personalized, with consideration of the level of obesity, presence of obesity-related complications, other comorbidities, age, and body fat distribution (Figure 2). The rational approach is to provide multidisciplinary management of obesity and a treatment goal of a 5–10% reduction in bodyweight over 6–12 months (14, 15, 19).

There are three strategies for overweight/obesity management: **non-pharmacological interventions, pharmacological interventions, and metabolic surgery**. If the BMI is above 25 kg/m^2, non-pharmacological measures are mandatory. The use of anti-obesity medications, in addition to lifestyle interventions, is indicated for people with obesity (BMI ≥ 30 kg/m^2) or those who are overweight (BMI ≥ 27 kg/m^2) with at least one weight-related health condition (e.g., type 2 diabetes, hypertension, dyslipidemia, cardiovascular disease). Bariatric surgery might be considered if previous measures have failed in people with obesity. BMI values should be interpreted carefully, as misclassification might occur in very muscular or frail people. Certain ethnic groups, notably Asian populations, have lower BMI cutoffs used to classify overweight and obesity due to differences in body composition and cardiometabolic risk (15, 19).

Regardless of the strategy used to lose weight, even a small body weight reduction could be beneficial. Probably the best-known clinical benefit of weight loss is observed in patients with type 2 diabetes. Even a small weight loss (about 3–7% of baseline weight) improves glycemia and most of the cardiovascular risk factors. Greater, sustained weight loss (> 10%) is associated with higher positive impacts, such as disease-modifying effects and possible remission of type 2 diabetes, as well as improved long-term cardiovascular outcomes and reduced mortality (19–21).

It is important to discuss the approach to combating iatrogenic obesity. Many commonly used medications, such as antipsychotics (e.g., clozapine, olanzapine, and risperidone), some antidepressants (e.g., mirtazapine and paroxetine), certain antiepileptic drugs (e.g., pregabalin and valproate), and glucocorticoids, might promote weight gain. Whenever possible, the use of such drugs should be minimized, especially

in patients with type 2 diabetes and/or cardiovascular diseases. If there is no suitable alternative, intensified lifestyle interventions might minimize drug-related adverse weight impacts (19, 22). In order to achieve the best and long-lasting results when counseling on behavioral changes, intervention alternatives, and weight management goals, shared decision-making should be adopted.

Non-pharmacological interventions

Although we aimed to discuss only pharmacological interventions in this article, the most important issue when it comes to successful weight control is to highlight the importance of lifestyle interventions. Non-pharmacological measures are essential and compatible with other weight-control strategies. Lifestyle interventions consisting of a reduced-calorie diet (about 500 kcal/day of energy deficit), increased physical activity (> 200 min/week), and behavior therapy can lead to up to 8% mean weight loss (of the initial weight) over 6 months. This effect is comparable to that obtained with moderate-efficacy anti-obesity medication, so it should not be underestimated. It is recommended to insist on a minimum of 6 months of high-intensive, comprehensive lifestyle interventions to provide long-lasting weight control (19, 23). A personalized approach, including a diet prepared according to the person's preferences, nutritional needs, religious attitudes, and socioeconomic status, as well as individualized physical activity, guarantees the best results. Unfortunately, after a follow-up of 4 to 7 years, the patients regained most of the weight they had lost, according to a meta-analysis of 14 different intervention trials evaluating the efficacy of diet and exercise for weight management (24).

Pharmacological interventions

Pharmacotherapy is generally intended for patients who have not responded to lifestyle interventions, as certain anti-obesity drugs might provide greater weight loss. Although obesity is a chronic disease with very serious complications, anti-obesity medications remain underused. Disease-related stigmatization and an unfavorable history of anti-obesity medications are partly responsible for suboptimal obesity management.

Most of the anti-obesity medications developed so far have not been approved or have had to be withdrawn from the market due to some safety concerns. Some of the anti-obesity medications that reached regulatory approval but were soon after withdrawn are (14):

- **Sibutramine**, a serotonin and noradrenaline reuptake inhibitor, is associated with cardiovascular risk;
- **Fenfluramine** and **dexfenfluramine** potentiate central serotonergic transmission, and are associated with cardiac valvulopathy and pulmonary hypertension;
- **Rimonabant**, a selective cannabinoid receptor-1 antagonist, is linked to suicidal risk;
- **Methamphetamine**, a psychostimulant and sympathomimetic drug, is linked to an enhanced likelihood of drug dependence and abuse;
- **Lorcaserin,** a highly selective $5HT_{2C}$ receptor agonist, was most recently removed from the market due to an increased risk of cancer.

Thus, it is not surprising that anti-obesity drugs have garnered a bad reputation over time. The “perfect” anti-obesity drug should provide sizable and sustainable weight loss, possibly have a beneficial impact on cardiovascular and other comorbidities, and be devoid of the potential for abuse. Not so long ago, this idealized drug prototype seemed like an insurmountable challenge. But it seems that the agonists of the GLP-1 receptor broke the bad luck of anti-obesity drugs.

The relevant regulatory agencies, the Food and Drug Administration (FDA) and the European Medicines Agency (EMA), set up novel, stringent criteria for a drug to be approved for the treatment of obesity. As a *primary efficacy endpoint*, the new drug must induce statistically significant **placebo-adjusted weight loss of at least 5%** (of baseline weight) after 12 months of treatment. Therefore, treatment with certain anti-obesity drug should be discontinued after 12 months if patients have been unable to lose at least 5% of their initial body weight. *Secondary efficacy endpoints* are also mandatory and include measurement of central adiposity, influence on cardiovascular risk factors (blood pressure, hyperglycemia, and dyslipidemia), and cardiovascular morbidity/mortality (20, 21).

Approved anti-obesity medications

Six anti-obesity drugs (orlistat, phentermine/topiramate, naltrexone/bupropion, liraglutide, semaglutide, and tirzepatide) are currently approved by regulatory authorities (EMA and/or FDA) for long-term (> 12 weeks) obesity management (Table I). Most of the currently approved anti-obesity drugs, except orlistat, primarily act centrally by reducing appetite, increasing satiety, and/or reducing food reward. Meltreleptin and setmelanotide are indicated for rare obesity syndromes. An increased pool of anti-obesity medications approved up to date is helpful to both clinicians and patients to set more realistic and achievable goals.

The assessment of efficacy and safety should be done at least monthly for the first 3 months upon initiating an anti-obesity drug, and at least quarterly thereafter. Based on the available clinical data, it seems that early responders have better long-term results. Furthermore, the latest approved anti-obesity medications have a far greater response rate (25).

Table I Approved anti-obesity medications: clinical efficacy and safety profile (26, 28, 33, 38, 43, 46, 49)

Tabela I Odobreni lekovi za lečenje gojaznosti: klinička efikasnost i bezbednosni profil (26, 28, 33, 38, 43, 46, 49)

Drug (dose, route of administration)	Regulatory approval	Administration schedule	Clinical efficacy* (reference)	Side effects (very common/ common)	Contraindications	Special considerations
Orlistat (120 mg, *oral*)	EMA 1998 FDA 1999	120 mg/3x/day	**~3%** (Finer *et al.*, 2000)	Abdominal pain, fecal urgency, oily spotting, liquid stools, flatulence, upper respiratory infections	Pregnancy Breastfeeding Cholestasis Chronic malabsorption syndrome	Inexpensive Adherence to a specific diet Prone to drug interaction Malabsorption of fat-soluble vitamins
Phentermine/ Topiramate ER (3.75/23, 7.5/46, 11.25/69, and 15/92 mg, *oral*)	FDA 2012	3.75/23 mg, once daily for 14 days; monthly titration upwards to achieve weight loss	**8.6%** (Gadde *et al*., 2011)	Paresthesia, dizziness, dysgeusia, insomnia, constipation, dry mouth *In pediatrics*: depression, arthralgia, ligament sprain	Pregnancy Glaucoma Hyperthyroidism MAOI within 14 days	Embryo-fetal toxicity Increase in blood pressure and heart rate Possible mood, sleep, and cognitive disorders Suicidal ideation
Naltrexone/ Bupropion PR (8/90 mg or 7.2/72 mg**, *oral*)	FDA 2014 EMA 2015	Upwards titration over 4 weeks to maximum of two tablets twice daily	**~5%** (Greenway *et al*., 2010)	Nausea, vomiting, constipation, headache, dizziness, dry mouth, diarrhea	Uncontrolled hypertension Seizures and bipolar disorders Anorexia nervosa or bulimia Chronic opioid use MAOI within 14 days Discontinuation of alcohol or benzodiazepines	Seizures Prone to drug interactions Increase in blood pressure and heart rate Hypersensitivity reactions Suicidal ideation Neuropsychiatric symptoms Hepatic and renal impairment
Liraglutide (3 mg, *subcutaneous*)	FDA 2014 EMA 2015	Start with 0.6 mg, once daily for 7 days; titrate upwards weekly to max 3 mg/daily	**~5.5%** (Pi-Sunyer *et al*., 2015)	Nausea, vomiting, headache, hypoglycemia, diarrhea, constipation dyspepsia abdominal pain, fatigue, dizziness, increase in lipase/amylase levels	Hypersensitivity to active substance or any of the excipients Personal or family history of medullary thyroid cancer and multiple endocrine neoplasia type 2***	Injectable form Thyroid adverse effects Acute pancreatitis Hypoglycemia in T2D Gallbladder disease Increase in heart rate Dehydratation Diabetic retinopathy in T2D (with semaglutide)
Semaglutide (2.4 mg, *subcutaneous*)	FDA 2020 EMA 2021	Start with 0.25 mg, once weekly; titrate upwards weekly to max 3 mg	**12.5%** (at 68 week) (Wilding *et al*., 2020)			
Tirzepatide (5-15 mg, *subcutaneous*)	FDA 2022 EMA 2022	Start with 2.5 mg, once weekly; titrate upwards weekly to max 15 mg	**~18%** (Jastreboff *et al*., 2022)			

*Placebo-adjusted weight loss after 1 year (unless otherwise stated) of treatment with the maximum tolerated dose(s);

**Dosage form approved in the EU

***Contraindication by the FDA but not by the EMA

EMA, European Medicines Agency; ER, extended-release; FDA, Food and Drug Administration; PR, prolonged-release; T2D, type 2 diabetes

1. Orlistat

Orlistat is an anti-obesity drug with the longest license for long-term use. This drug is prescribed for adults and adolescents ≥ 12 years of age, in addition to a reduced-calorie diet. It is also available as an over-the-counter product (26).

Mechanism of action. Orlistat, as an inhibitor of gastric and pancreatic lipases, decreases the absorption of intestinal triglycerides by about 30–35%. Inhibiting the breakdown of triglycerides into absorbable monoglycerides and free fatty acids reduces calorie intake. Thus, orlistat promotes a negative caloric balance. Orlistat has little impact on weight loss with non-fatty food consumption (1, 27).

Clinical efficacy in weight loss. As one of the oldest representatives of the class, it is not extensively evaluated. Inconsistent results are reported about its efficacy in weight loss. One study showed that patients receiving orlistat in conjunction with a low-energy diet had an average loss of about 8.5% of their initial body weight, compared with 5.4% for placebo-treated patients. In the orlistat group, 35% of patients achieved at least a 5% weight loss (compared with 21% in the placebo group) (28).

Clinical efficacy beyond weight loss. Orlistat has been shown to reduce serum levels of total and LDL cholesterol, while also improving the LDL/HDL ratio. These effects might exceed those anticipated from weight loss (28). Another beneficial issue is extracted from the XENDOS (XENical in the prevention of Diabetes in Obese Subjects) trial, the largest randomized controlled study that evaluated the effect of orlistat in 3,305 people with obesity, where it was found that this drug reduces the incidence of type 2 diabetes by about 37%. In the same study, orlistat positively impacted blood pressure, insulin sensitivity, and lipid profile (29).

Safety profile. The main complaints are gastrointestinal disturbances. Among the common adverse effects of orlistat are abdominal pain/discomfort, oily spotting, fecal urgency, fatty/oily stools, flatulence, liquid stools, headache, and upper respiratory infections (Table I). Gastrointestinal discomfort tends to diminish over time. It can be minimized by adhering to a low-fat diet and taking a fiber supplement along with it. Orlistat may significantly reduce the absorption of fat-soluble vitamins A, D, E, and K. To prevent possible deficiencies, supplementation could be considered for high-risk patients. The use of an additional contraceptive method might be needed to prevent a possible failure of oral contraception in the case of severe diarrhea (26, 28, 29).

Orlistat's popularity as an anti-obesity drug has decreased due to its undesirable side effects and very modest weight loss capacity. It could still be considered for patients who cannot tolerate centrally acting appetite suppressants, particularly those with impaired fasting glucose and hyperlipidemia.

2. Phentermine/topiramate

Phentermine/topiramate was the first officially approved drug combination by the FDA for long-term treatment of obesity. However, the EMA has not approved this product because of many safety concerns, such as abuse potential, the lack of long-term

data on the cardiovascular effects of phentermine, and cognitive disfunction associated with topiramate (30). Due to a paucity of long-term studies, phentermine monotherapy has restricted FDA approval for short-term use (duration is not specified but often interpreted as < 3 months) in obesity control, alongside diet and exercise. Topiramate is licensed as a monotherapy for the treatment of partial and generalized seizures, as well as for migraine prophylaxis.

Mechanism of action. The exact mechanism of the anorexigenic effect of this drug combination is still unknown. Phentermine is a sympathomimetic drug that inhibits noradrenaline reuptake in several brain regions, including the hypothalamus, but also increases the release of dopamine to a lesser extent than amphetamines. This probably leads to a suppressed appetite and decreased food consumption (31). Topiramate has multiple proposed mechanisms of action. It enhances GABAergic neurotransmission, blocks sodium channels, inhibits carbonic anhydrases, and acts as an antagonist at the ionotropic glutamate receptors (31). Several mechanisms of action of topiramate-induced weight loss have been postulated, including modulation of the food reward system, activation of lipoprotein lipase, and the reduction of leptin and blood glucose levels (32).

Clinical efficacy in weight loss. This combination provides robust weight-loss potential. In the CONQUER one-year study on 2,487 participants with a BMI of 27–45 kg/m^2 and more than two obesity-related comorbidities, the following results were observed: 1.2% in the placebo group, 7.8% in the phentermine/topiramate 7.5/46 mg group, and 9.8% in the phentermine/topiramate 15/92 mg group. With the highest dose of the phentermine/topiramate combination, 70% of patients achieved at least a 5% weight loss (compared with 21% in the placebo group) (33). The findings of this study enabled the approval of phentermine/topiramate by the FDA. When compared to monotherapy with either drug alone, the drug combination resulted in greater weight loss and a better adverse effect profile (34).

Clinical efficacy beyond weight loss. When it comes to the secondary endpoints, patients taking this drug combination had statistically significant improvements in their lipid and glycemic profiles, blood pressure, and waist circumference. In addition, phentermine/topiramate plus lifestyle modification markedly reduced progression to type 2 diabetes in patients with increased BMI and prediabetes/metabolic syndrome (35). Topiramate has shown benefit in patients with emotional eating and binge-eating disorders, but it is not currently approved as a monotherapy for obesity (36).

Safety profile. The safety concerns are the main reason why the EMA decided to refuse the drug approval. Common adverse effects of phentermine/topiramate include insomnia, paresthesia, dizziness, dry mouth, dysgeusia, and constipation (1, 26), which are mostly acceptable (Table I). To prevent insomnia, this medication should be taken in the morning. Phentermine itself is associated with increased cardiovascular risk and certain abuse potential. The highest safety concerns of topiramate are teratogenicity and cognitive/psychiatric disorders as well. Advice on contraceptive planning is important before starting this drug for women of childbearing age. Topiramate may, however,

impair the effectiveness of oral contraceptives, although this is unlikely at doses lower than 200 mg daily (37).

3. Naltrexone/bupropion

Naltrexone/bupropion is another drug combination approved for the long-term treatment of overweight/obesity. Each component of this product has been used in other medical conditions: naltrexone to treat alcohol use disorders and opioid dependence, while bupropion is approved for the management of depression and smoking cessation (FDA and EMA).

Mechanism of action. Bupropion is a dopamine- and noradrenaline-reuptake inhibitor. It also activates the anorexigenic pro-opiomelanocortin neurons in the hypothalamus. This way, it suppresses appetite. By adding naltrexone, which blocks opioid receptor-mediated inhibition of proopiomelanocortin neurons, sustained appetite reduction is expected. Thus, this combination reduces both food intake and satiety in a synergistic way. Naltrexone/bupropion combination could also reduce reward-related eating behavior, as dopamine regulates the desire for eating and opioids convey the reward-related sensation of eating palatable foods (1, 14).

Clinical efficacy in weight loss. In one of the largest clinical studies, COR (Contrave Obesity Research)-I, which included individuals with a BMI $\geq$ 30 kg/m^2 or a BMI $\geq$ 27 kg/m^2 with at least one weight-related comorbid condition (hypertension or dyslipidemia), the percent weight loss observed with naltrexone/bupropion 32/360 mg for 56 weeks was 6.1%, compared to placebo 1.3%. Nearly 50% of participants assigned to the naltrexone/bupropion combination had a decrease in body weight of more than 5%, compared to 16% of placebo-treated subjects (38). Subsequent studies reported a similar result of an about 5% placebo-adjusted weight loss with naloxone/bupropion.

Clinical efficacy beyond weight loss. The naloxone/bupropion combination might exert a beneficial impact on cardiometabolic risk. Patients treated with this medication report a marked reduction in waist circumference, triglycerides, fasting insulin, and increased HDL-cholesterol levels (38). In patients with food addiction and obesity, the naloxone/bupropion combination could be of particular benefit (39).

Safety profile. Typical side effects of this drug combination include headache, dizziness, dry mouth, and gastrointestinal disturbances (nausea, vomiting, constipation, or diarrhea). To reduce gastrointestinal discomfort, naltrexone/bupropion doses should be increased gradually (Table I). Although naltrexone/bupropion might minimize some cardiovascular risk factors, its cardiovascular safety remains uncertain. Thus, caution is needed if it is administered to patients with coronary disease or stroke (40). A complex psychiatric impact has been observed, meaning an increased prevalence of anxiety and sleep disorder, with an improvement of co-existing depression (41). Additionally, naltrexone-bupropion is associated with several clinically relevant drug interactions, given that bupropion is an inhibitor of CYP2D6 enzymes. Thus, it might increase the blood levels of aripiprazole, duloxetine, escitalopram, fluoxetine, sertraline or metoprolol (26).

4. Liraglutide

Liraglutide is the first injectable anti-obesity medication. It belongs to a class of hypoglycemic drugs known as glucagon-like peptide 1 (GLP-1) receptor agonists. Liraglutide is approved for weight management at a dose of 3 mg/daily in patients from the age 12 and above, upon previous approval for diabetes type 2 treatment at a lower dose (1.8 mg/daily) (26).

Mechanism of action. Liraglutide mimics the action of endogenous GLP-1, an incretin hormone secreted from enteroendocrine cells in the gut in response to food consumption. It has numerous biological effects, including increasing insulin secretion while inhibiting glucagon release from pancreatic beta-cells, slowing stomach emptying, and decreasing appetite. The liraglutide anorexigenic mechanism of action might be explained by central control of appetite and food consumption through GLP-1 receptor agonism in the hypothalamus, brainstem, and limbic reward system, as well as by peripheral actions on slowing gastric emptying (increased postprandial satiety and fullness) (1, 42). Compared to human GLP-1, liraglutide has a much longer half-life (13 hours *vs.* a few minutes) due to its stronger plasma protein binding and lower susceptibility to enzymatic breakdown.

Clinical efficacy in weight loss. The main study that led to liraglutide approval as an anti-obesity drug was the SCALE (Satiety and Clinical Adiposity Liraglutide Evidence) Obesity and Prediabetes trial. This study enrolled patients with overweight/obesity without diabetes, of whom 2,487 received liraglutide 3 mg and 1,244 were on placebo, in addition to lifestyle modification. After 56 weeks, a total weight loss of 8% was achieved in the liraglutide group (*vs.* 2.6% in the placebo group), of which 63% (*vs.* 27% in the placebo group) have lost ≥5% of their body weight (43). Comparable results were noted in subsequent studies.

Clinical efficacy beyond weight loss. Liraglutide definitely broke the bad luck of anti-obesity medications when it comes to cardiovascular safety. Indicators of increased cardiovascular risk, including blood pressure, increased HbA1c and non-HDL cholesterol, and decreased HDL-cholesterol, were significantly improved in patients without diabetes/cardiovascular disease treated with liraglutide (43). Liraglutide's beneficial effects on cardiovascular outcomes in people with obesity and concurrent type 2 diabetes are among its primary advantages. Liraglutide's therapeutic value extends from endocrinologic to cardiovascular morbidity, as it has been shown to lower the risk of major cardiovascular events in patients with or without a history of myocardial infarction or stroke (44) (Table I).

Safety profile. The most frequent side effects of liraglutide are nausea, vomiting, diarrhea, constipation, and dyspepsia. The majority of patients tolerate it well (26). Although patients might have an increased level of amylase and lipase, the risk of acute pancreatitis is considered to be low (30). It is important to note that the risk of thyroid cancers has been revised and is now considered unfounded. Thus, the EMA has removed thyroid cancers from the list of official contraindications (26, 45). Liraglutide is a good

option for patients with a high BMI and mental disorders, since there have been no reports of neuropsychiatric safety concerns.

5. Semaglutide

Semaglutide, another GLP-1 receptor agonist, has been demonstrated to have the greatest impact among hypoglycemics on body weight in patients with type 2 diabetes, which led to its clinical evaluation in patients with a high BMI without diabetes. This population's mean weight loss was about 15% of the initial body weight, obtained with a higher dose of semaglutide. It was the greatest weight loss ever accomplished with certain anti-obesity medications. Semaglutide is approved for weight management at a dose of 2.4 mg/weekly in patients aged 12 and above, while a lower dose of up to 1 mg/weekly is approved for type 2 diabetes treatment (26).

Mechanism of action. As stated with liraglutide, semaglutide acts on those parts of the hindbrain and hypothalamus that are involved in promoting satiety and decreasing rewarding signals, but it also has peripheral effects.

Clinical efficacy in weight loss. Semaglutide definitely bridges the gap between preferred and achieved weight loss, which has been proven in numerous clinical trials on patients with overweight/obesity with or without concomitant diabetes or cardiovascular conditions. In the STEP 1 trial, which enrolled 1,961 participants with overweight/obesity and without comorbidities, the mean percent of weight loss was 14.9% with semaglutide (at a dose of 2.4 mg/weekly for 68 weeks) *versus* 2.4% with placebo, combined with lifestyle modifications. More participants in the semaglutide group than in the placebo group achieved weight reductions of ≥5% (86.4 *vs.* 31.5%), ≥10% (69 *vs.* 12%), and ≥15% (50.5 *vs.* 4.9%) after 68 weeks (46).

Clinical efficacy beyond weight loss. Semaglutide significantly decreased HbA1c, blood pressure, fasting glucose, and waist circumference (cardiometabolic risk markers) when compared to placebo. Remarkably, there was no positive effect on the lipid profile (46). In one of the largest clinical trials (SELECT) evaluating the impact of semaglutide on cardiovascular outcomes, 17,604 patients with overweight or obesity, without diabetes, but with established cardiovascular disease, were enrolled. Semaglutide reduced the incidence of nonfatal myocardial infarction/stroke and death from cardiovascular causes by about 20% (47). Furthermore, semaglutide markedly enhanced the quality of life in patients with obesity-related heart failure with preserved ejection fraction (HFpEF); however, it remains unclear if this beneficial effect is only a result of a drop in body weight. According to Capone and collaborators, incretin-based medications may provide a revolutionary treatment for obesity-related HFpEF (48).

Safety profile. Gastrointestinal disturbances (nausea, diarrhea, vomiting, and constipation) were the most frequently reported adverse reactions to semaglutide. Most of them are mild-to-moderate in severity, transient, and tend to resolve over time. No increased risk of developing any type of cancer has been noted, nor has suicidal ideation been associated with semaglutide use (26, 46). In patients with diabetic retinopathy

receiving semaglutide, there has been evidence of an elevated risk of deterioration of this microvascular complication (26) (Table I).

6. Tirzepatide

Tirzepatide belongs to the latest generation of anti-obesity medications. Almost immediately upon its registration as an antidiabetic, tirzepatide got a license for obesity treatment. Tirzepatide quickly gained the title of the "blockbuster drug" for the treatment of obesity, indicating that it is more effective than all other licensed drugs.

Mechanism of action. Tirzepatide is a combined GLP-1 and GIP agonist. It shares the same mechanisms of action as liraglutide and semaglutide. However, as a GIP agonist, tirzepatide additionally reduces satiety and energy intake, but might increase energy expenditure as well (1).

Clinical efficacy in weight loss. Tirzepatide captured the attention of the anti-obesity dedicated audience with the SURMOUNT-1 study. This study involved more than 2,500 adults with obesity or overweight and at least one weight-related health issue. At the end of the study (which lasted for 72 weeks), the mean weight loss was: 15%, 19.5%, and 20.9% for the doses of tirzepatide of 5, 10, and 15 mg, respectively, and 3.1% for the placebo group. The percentage of participants who had a weight reduction of ≥5% was 85%, 89%, and 91% with 5, 10, and 15 mg of tirzepatide, respectively, and 35% with placebo. Of them, 50% (10 mg) and 57% (15 mg) of participants achieved a reduction in body weight of ≥20%, as compared with 3% in the placebo group (49).

Clinical efficacy beyond weight loss. When comparing the tirzepatide to the placebo group, the secondary endpoints of the SURMOUNT-1 trial, including blood pressure, waist circumference, glycoregulation, and lipid status, showed a substantial improvement. The magnitude of these improvements probably outweighs the effects on body weight reduction (49). In people with obesity, whether or not they have diabetes, tirzepatide lowers the risk of atherosclerotic cardiovascular disease (50). Studies evaluating its potentially beneficial impact on manifested coronary disease or HFpEF are ongoing.

Safety profile. The most common side effects of tirzepatide include gastrointestinal problems such as nausea, diarrhea, constipation, and vomiting. Those side effects were generally mild or moderate in severity and are surmountable in patients (26, 49).

GLP-1 receptor agonists misuse and postmarketing surveillance

Soon after being put on the market, semaglutide became a "magic bullet" for rapid weight loss. Many celebrities and social media influencers shared their glowing weight-loss reviews, supporting the *off-label* use of semeglutide. The *Wegovy*® frenzy by people who wanted to lose weight but had no medical reason to take it led to its shortage on the market. Many of them turned to *Ozempic*® to continue their weight loss journey, which contributed to its global deficit, as well as the increased circulation of falsified versions. Falsified medical products have low efficacy and/or suspicious safety. Therefore, several

issues need to be pointed out: the prescriptions for *Ozempic*® should be limited to people with diabetes; *Wegovy*® should not be used out of the indications; and laypersons should refrain from making medical statements on social media. The same scenario could be expected with tirzepatide, so unauthorized use of medicinal products containing GLP-1 receptor agonists should be highly discouraged.

The gain in "popularity" of GLP-1 receptor agonists was followed by certain safety concerns, especially in the psychiatric domain, such as thoughts of self-harm and suicide. Such a risk may probably be ruled out, even though it cannot be completely excluded (51). Special caution is warranted when prescribing GLP-1 receptor agonists to patients with co-existing psychiatric disorders (52). Further research is needed to elucidate the psychiatric portfolio of incretin mimetics, which may even be beneficial as their antidepressive properties have also been proposed (53).

Medications on the horizon

Several medications have reached the final step in the clinical evaluation (phase 3) as potential anti-obesity medications. Some of them are (1, 14, 54):

- **Methylphenidate** (a stimulant approved for the treatment of attention deficit hyperactivity disorder) acts as a dopamine reuptake inhibitor that is suggested to reduce energy intake.
- **Tesofensine** is a noradrenaline, serotonine, and dopamine reuptake inhibitor that suppresses appetite and might positively impact reward-related food intake. The main health concern with this drug is the possible cardiovascular risk.
- **Exenatide**, a GLP-1 receptor agonist, is being exploring for obesity treatment in patients without diabetes. A combination of **exenatide and dapagliflozine** (sodium-glucose cotransporter-2 inhibitor) is also in the last stage of evaluation in patients with obesity and prediabetes.
- **Dapagliflozine and metformin** is another drug combination that is being evaluated for efficacy against overweight in patients with newly diagnosed diabetes or prediabetes.
- **Canagliflozine and phentermine** are drugs that combine an energy loss effect due to glycosuria with an appetite suppressor to overcome compensatory hyperphagia/increased appetite due to glucose secretion.
- **Cagrilintide** is an amylin analogue that increases satiety signalling at central levels and reduced gastric emptying at periphery. It is being evaluated in **combination with semaglutide**.

Numerous drugs/drug combinations are in the pipeline for future medication for obesity. Among them there are novel dual GLP-1/GIP agonists (e.g., cotadutide), triple GLP-1/GIP/glucagone agonists (e.g., retatrutide), glucagone analogues, amylin receptor agonists, leptin sensitisers and many others (14, 54).

Treatment selection

In the selection of the anti-obesity medication to start therapy with, it is important to consider both the features of the drug and the patient as well. When it comes to the drug profile, the crucial factors are weight-reducing capacity and safety issues (adverse effect profile and contraindications). From the patient's perspective, the present comorbidities and the person's age are the most important. In patients with diabetes, the preferred pharmacotherapy for obesity should be a GLP-1 receptor agonist or dual GLP-1/GIP receptor agonist with greater weight loss efficacy (i.e., semaglutide and tirzepatide). If the patient has cardiovascular comorbidity, the agonists of the GLP-1 receptor (i.e., semaglutide and liraglutide) should be taken into account, given their proven cardiovascular benefits. The patient's preferences and limitations should also be considered.

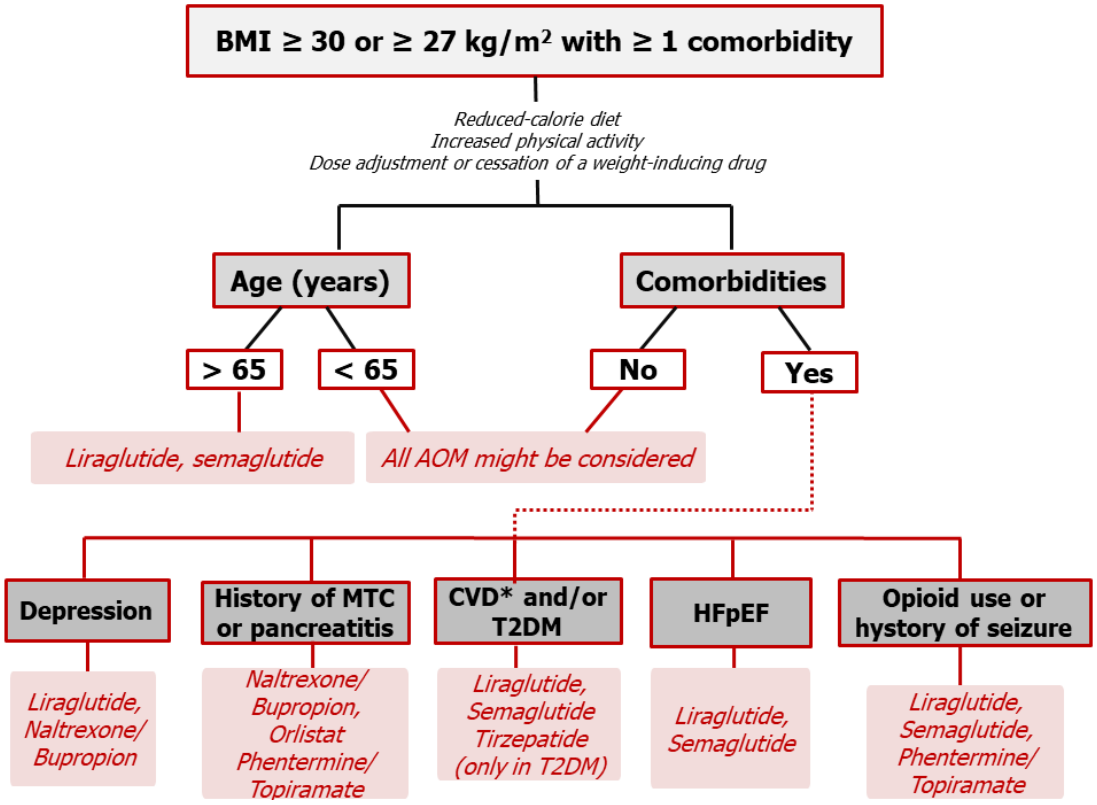

Figure 2. Suggested algorithm for the selection of anti-obesity medications (*prepared according to References no. 1 and 26*)
AOM, anti-obesity medications; CVD, cardiovascular disease and high cardiovascular risk; HPpEF, heart failure with preserved ejection fraction; MTC, medullary thyroid carcinoma; T2DM, type 2 diabetes.

Slika 2. Predloženi algoritam za izbor leka za lečenje gojaznosti (*pripremljeno prema Referencama br. 1 i 26*)
AOM, lekovi za lečenje gojaznosti; CVD, kardiovaskularne bolesti i visok kardiovaskularni rizik; HPpEF, srčana slabost sa očuvanom ejekcionom frakcijom; MTC, medularni karcinom štitaste žlezde; T2DM, dijabetes tip 2.

In older people (> 65 years), there is muscle loss related to aging, chronic diseases, and poor nutrition, which makes the treatment of obesity more challenging. Up to now, GLP-1 receptor agonists (semaglutide and liraglutide) could be preferred in this age group since they do not cause cardiovascular or cognitive side effects; on the contrary, they may improve them. Semaglutide and liraglutide are also preferrable in adolescent population (12–18 years). Long-term maintenance of weight loss is still challenging for most people. Figure 2 presents the suggested algorithm for the selection of anti-obesity drugs.

Conclusions

For people living with obesity, weight loss is often a difficult journey that requires cardinal lifestyle changes. Pharmacotherapy for obesity is an adjunct therapy for patients whose response to lifestyle interventions alone is insufficient. There is no “one size fits all” approach to the pharmacotherapy of obesity. More substantial weight loss is associated with greater clinical utility. The highest body weight reduction of more than 10% of the initial body weight may be achieved with semaglutide and tirzepatide. If cardiovascular disease or diabetes is present, priority should be given to semaglutide or liraglutide. Thus, an incretine-based approach combats both overweight/obesity and weight-related cardiometabolic comorbidities.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Author contributions

Katarina Sićović: Writing - original draft; **Ana Micov:** Conceptualization, Supervision, Writing - review & editing.

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Farmakoterapija gojaznosti: *danas i sutra*

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Kratak sadržaj

Gojaznost je hronična, progresivna i recidivirajuća bolest. Prevalencija gojaznosti dostiže pandemijske razmere, baš kao i komorbiditeti povezani sa gojaznošću poput dijabetesa, kardiovaskularnih bolesti i izvesnih karcinoma. Glavni cilj lečenja gojaznosti je smanjenje rezidualnog morbiditeta. Farmakoterapija je namenjena pacijentima koji nisu odgovarajuće reagovali na izmenu životnog stila. Trenutno je šest lekova odobreno za dugoročno lečenje gojaznosti (orlistat, fentermin/topiramat, naltrekson/bupropion, liraglutid, semaglutid i tirzepatid). Većina njih, osim orlistata, pretežno deluje centralno povećanjem osećaja sitosti, kao i smanjenjem apetita i hranom izazvanog „nagrađivanja". Najveću efikasnost u redukciji povišene telesne mase (preko 10%) ostvaruju semaglutid i tirzepatid. Iako su svi lekovi za lečenje gojaznosti pokazali povoljan uticaj na kardiometaboličke faktore rizika, samo je za liraglutid i semaglutid pokazano da smanjuju rizik od velikih kardiovaskularnih događaja kod pacijenata sa ili bez potvrđene kardiovaskularne bolesti. Personalizovani pristup, koji uzima u obzir karakteristike leka (efikasnost u smanjenju telesne mase i bezbednost leka) i karakteristike pacijenta (komorbiditeti, starost i preferencije), garantuje najbolje rezultate. U ovom radu ćemo se kritički osvrnuti na efikasnost i bezbednost trenutno odobrenih lekova za lečenje gojaznosti i onih koji su u finalnoj fazi kliničkog ispitivanja.

Ključne reči: liraglutid, semaglutid, tirzepatid, personalizovan pristup