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Modern Approaches to Obesity Treatment – literature review

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Abstract

Introduction and Purpose:

Obesity constitutes a complex health issue of an epidemiological nature, affecting an increasing number of individuals globally. It is associated with numerous health complications, including cardiovascular diseases, type 2 diabetes, hypertension, as well as mental health disorders and a reduced quality of life. The treatment of obesity is a multifaceted process that should encompass lifestyle modifications such as dietary improvement, enhanced physical activity, and psychological support. In certain cases - depending on the severity of obesity and the presence of comorbid conditions - it may become necessary to implement pharmacotherapy or surgical interventions, such as bariatric procedures. This article provides a comprehensive overview of the condition of obesity and its underlying causes. Furthermore, the epidemiology of the phenomenon is presented. The primary focus, however, is placed on the available pharmacological solutions that may assist in combating obesity.

Summary:

At present, alongside the modification of dietary habits and the enhancement of physical activity, the use of pharmacological agents is becoming an increasingly significant component of obesity therapy. These medications primarily contribute to the reduction of appetite and the limitation of fat absorption, thereby supporting the overall effectiveness of the treatment process.

Keywords: *obesity*; *obesity treatment*; *causes of obesity*; *liraglutide*; *phentermine*

Definition of Obesity and Classification Criteria

Obesity is a condition characterized by the excessive accumulation of adipose tissue in the body, which may result in adverse health consequences. According to the World Health Organization (WHO), obesity constitutes a complex health issue arising from the interaction of various factors, including genetic predisposition, lifestyle, diet, physical activity levels, and psychosocial determinants. One of the most commonly used tools for assessing overweight and obesity is the Body Mass Index (BMI), which is calculated by dividing an individual's weight in kilograms by the square of their height in meters, in accordance with the following formula:

$$BMI = \frac{weight\ [kg]}{(height\ [m])^2}$$

In the context of adults, overweight is defined as a Body Mass Index (BMI) ranging between 25.0 and 29.9 kg/m². Conversely, obesity is diagnosed when the BMI reaches 30 kg/m² or higher (see Table 1). These thresholds, established by the World Health Organization, serve as standardized criteria for the classification of body weight and the associated health risks, thereby facilitating both clinical assessment and public health surveillance.

Table 1. BMI Classification with Reference Ranges [1]

BMI Classification	**BMI Range [kg/m²]**
Underweight	< 18,5
Normal weight	18,5 – 24,9
Overweight	25,0 – 29,9
Obesity Class I	30,0 – 34,9
Obesity Class II	35,0 – 39,9
Obesity Class III (severe or morbid obesity)	≥ 40,0

It is important to note that, in the case of children and adolescents, the assessment of overweight and obesity is based on different criteria than those used for adults. For children under the age of five, according to the World Health Organization (WHO) standards, overweight is defined as a weight exceeding the median height-for-age by at least two standard deviations [1, 2]. In the age group of 5 to 19 years, overweight is diagnosed when the BMI surpasses one standard deviation above the WHO median, whereas obesity is recognized when the BMI exceeds two standard deviations above that median [3, 4]. According to Kelly et al., obesity in adolescents aged 12 to 18 is diagnosed when the BMI reaches or exceeds the 95th percentile, adjusted for age and sex [5]. It should be emphasized that, although BMI is a valuable and widely used tool for assessing body weight, it does not account for important factors such as body fat percentage, fat distribution, or muscle mass. Therefore, in certain clinical situations, additional examinations or measurements may be required to obtain a more accurate and individualized assessment of a patient's health status. Women naturally have a higher percentage of body fat than men, a difference that is primarily attributable to biological and reproductive functions. Nevertheless, despite this physiological predisposition, the BMI values observed among women are typically lower [4, 6]. This discrepancy underscores the inherent limitations of the Body Mass Index as a sole diagnostic tool for evaluating health and physical condition. Crucially, BMI does not differentiate between abdominal (central) obesity and gluteofemoral (gynoid) obesity [4], both of which carry distinct metabolic implications. In light of these limitations, it is advisable to supplement BMI assessments with additional diagnostic methods, such as densitometric examinations, body composition analysis, waist circumference measurements, and the waist-to-hip ratio (WHR). These methodologies offer more nuanced and accurate insights into an individual's health status and the risk of developing weight-related disorders. Specifically, both waist circumference and the WHR - calculated as the ratio of waist to hip circumference - are important anthropometric indicators for assessing the presence of obesity and the associated risk of metabolic diseases. According to data reported in the literature, among the European population, a waist circumference exceeding 80 cm in women and 94 cm in men is indicative of obesity and is associated with an elevated risk of obesity-related health complications. Similarly, waist-to-hip ratio (WHR) values above 0.8 for women and 1.0 for men are likewise considered markers of increased risk for obesity, as well as a heightened likelihood of developing cardiovascular and metabolic disorders [4, 7].

These anthropometric thresholds are widely recognized in clinical practice as important indicators for early identification of individuals at risk and for the implementation of preventive and therapeutic interventions.

Causes of Obesity

Obesity is a complex health disorder with multifaceted etiologies that affect various dimensions of individual and public health. It results from an intricate interaction between genetic, metabolic, psychosocial, and environmental factors. This condition may be a consequence of biological determinants such as genetic predisposition, clinical disorders, and the administration of certain pharmacological agents that disrupt metabolic processes [8, 9]. Genetic factors play a significant role in the pathogenesis of obesity, influencing individual susceptibility to adipose tissue accumulation as well as the regulation of metabolism and appetite. It is noteworthy that heredity constitutes a major contributor to the development of obesity, potentially explaining why certain individuals are more prone to weight gain or experience greater difficulty in maintaining a healthy body weight despite the adoption of appropriate lifestyle interventions. Empirical studies have demonstrated that when one parent is affected by obesity, the likelihood of the child becoming obese increases four- to fivefold. This risk escalates dramatically - up to thirteenfold - if both parents are obese [9, 10, 11].

These findings underscore the importance of considering genetic and familial factors when evaluating the etiology and course of obesity, as well as when formulating personalized preventive and therapeutic strategies. Obesity exhibits a polygenic nature, meaning that multiple genes contribute to the development of this condition. Advances in human genome research have significantly facilitated the identification of numerous genetic loci associated with obesity, thereby confirming the substantial role that genetics plays in its pathogenesis. It is particularly noteworthy that more than 500 loci have been identified as genomic regions influencing various biological mechanisms, including the regulation of appetite, metabolic processes, and the function of adipocytes (fat cells) [4, 12, 13]. Polygenic obesity involves the cumulative effect of many genetic variants, each contributing modestly to the overall phenotype. These variants influence neuroendocrine pathways responsible for energy balance, satiety signaling, and fat storage. In contrast, monogenic theories of obesity focus on the effect of single-gene mutations that may independently result in severe, early-onset forms of obesity, often accompanied by endocrine or developmental abnormalities. Although monogenic forms are rare, their identification has deepened the understanding of the molecular and physiological pathways involved in energy homeostasis, providing valuable insights for potential therapeutic interventions. Among the genes associated with body weight regulation and the risk of developing overweight and obesity, several have been identified as playing pivotal roles in the complex neuroendocrine and metabolic mechanisms governing energy balance. These include:

- **FTO (Fat Mass and Obesity Associated Gene)** – This gene is one of the most extensively studied genetic determinants of obesity. Variants within the FTO locus are consistently associated with an increased risk of weight gain and higher body mass index. The presence of specific polymorphisms has been linked to elevated energy intake and impaired satiety signaling.

- **NPY (Neuropeptide Y)** – NPY functions as a neurotransmitter in the central nervous system and plays a key role in stimulating appetite and food consumption. Elevated levels of neuropeptide Y are associated with increased appetite and a propensity toward hyperphagia, thereby contributing to energy surplus and adiposity.
- **MC4R (Melanocortin 4 Receptor)** - This gene encodes a receptor involved in the central regulation of hunger and energy expenditure. Mutations in MC4R are one of the most common monogenic causes of obesity and are often associated with early-onset, severe obesity due to dysregulation of satiety and metabolic control.
- **MC3R (Melanocortin 3 Receptor)** - Similar to MC4R, this gene also encodes a receptor that plays a role in the modulation of appetite and energy homeostasis. Although less well-studied than MC4R, variants in MC3R have been implicated in altered energy balance and metabolic efficiency.
- **POMC (Proopiomelanocortin)** - This gene encodes a precursor protein that is cleaved into several active neuropeptides involved in the regulation of appetite and metabolism. Mutations in POMC may result in disrupted satiety signaling and are associated with severe obesity in rare cases.
- **PC1 (Prohormone Convertase 1, also known as PCSK1)** - This gene is crucial for the post-translational processing of prohormones into active hormones that regulate metabolism and appetite, such as insulin and proopiomelanocortin-derived peptides. Deficiencies or mutations in PC1 can lead to impaired hormonal signaling and subsequent metabolic dysfunction.
- **Leptin and the Leptin Receptor Genes** - Leptin is a hormone secreted by adipocytes that plays an essential role in signaling satiety and regulating energy expenditure. Mutations in the gene encoding leptin or its receptor can lead to leptin resistance or deficiency, both of which are associated with severe early-onset obesity due to the failure of the central nervous system to adequately respond to energy status signals. Collectively, these genetic components illustrate the highly polygenic nature of obesity and underscore the significance of genetic screening and personalized approaches in the prevention and management of obesity, particularly in individuals with a strong familial predisposition [4, 11, 13].

All of these genes and the metabolic pathways associated with them exert a significant influence on the risk of developing overweight and obesity, and their comprehensive understanding is essential for advancing research into metabolic disorders as well as for the formulation of effective prevention and treatment strategies. It is important to emphasize that mutations in genes implicated in monogenic forms of obesity - such as the *FTO* gene - have a substantial impact on the pathogenesis of this condition. The presence of specific allelic variants of the *FTO* gene has been shown to increase the risk of obesity by approximately 20–30%. Monogenic obesity typically manifests in childhood and may result in serious health consequences, including an elevated risk of cardiovascular diseases, type 2 diabetes, and other metabolic disorders [11].

It is of particular importance to note that the accumulation of adipose tissue in the human body may be associated with genetic syndromes that affect both metabolic function and hormonal regulation. Polygenic obesity constitutes a complex condition involving the interaction of numerous genes in conjunction with environmental influences. In contrast to monogenic obesity, which arises from a mutation in a single gene and typically results in early-onset and often severe manifestations, polygenic obesity is the outcome of the cumulative effect of multiple minor genetic variations. These variations, although individually of limited effect, collectively increase the predisposition to obesity. Among the genetic components potentially implicated in the development of polygenic obesity are mutations in beta-adrenergic receptor genes. Such mutations may disrupt normal regulatory mechanisms of lipolysis and thermogenesis, thereby promoting fat accumulation. Furthermore, mutations in the *SLC6A14* gene - which encodes a sodium- and chloride-dependent neurotransmitter transporter protein - may influence the metabolism of proteins and carbohydrates. Alterations in the function of this transporter can lead to metabolic imbalances that further contribute to an increased risk of obesity [11]. In the pathogenesis of obesity, particular attention must be paid to several genetically determined syndromes, such as Down syndrome, Laurence-Moon-Biedl syndrome, Prader-Willi syndrome, and Turner syndrome. These syndromic forms of obesity are often associated with a broad spectrum of endocrine and metabolic disturbances which, in consequence, contribute to either the development of obesity or the dysregulation of adipose tissue distribution and function [14]. Such syndromes typically involve complex genetic anomalies that disrupt normal hormonal signaling pathways, appetite regulation, and energy expenditure. In addition to genetic syndromes, a range of clinical disorders can also play a critical role in the etiology of obesity. These include neoplastic conditions, neuroinfections, and various forms of hormonal dysregulation. Endocrinopathies such as hypothyroidism, Cushing's syndrome, and polycystic ovary syndrome (PCOS) have been extensively documented as contributing factors to abnormal increases in body mass and changes in adipose tissue distribution [15, 16]. For instance, hypothyroidism may result in a decreased metabolic rate, thereby facilitating weight gain. Cushing's syndrome, characterized by excessive cortisol production by the adrenal glands, is particularly associated with central (abdominal) obesity and other features of metabolic syndrome [17, 18]. Pharmacological treatment is another contributing factor to weight gain and obesity. A variety of drugs have been identified as potential mediators of increased adiposity. These include antidepressants - particularly selective serotonin reuptake inhibitors (SSRIs), antipsychotics, antiepileptic drugs, hormonal contraceptives and hormone replacement therapies containing progesterone and estrogens, medications used in the management of diabetes (such as insulin and sulfonylureas), as well as anabolic steroids and corticosteroids [9, 13].

These agents may affect metabolic rate, appetite control, fat storage, and hormonal balance, thus enhancing the susceptibility to obesity, particularly in predisposed individuals. Epigenetics plays a significant role in understanding how environmental factors such as diet, lifestyle, stress, or exposure to toxic substances may influence the development of overweight and obesity.

In contrast to genetic changes, which affect the DNA sequence, epigenetic modifications pertain to the manner in which genes are regulated and expressed. Importantly, epigenetic changes occur through processes such as:

- **histone modification** – their modifications (acetylation, methylation) influence the level of chromatin condensation, which in turn regulates the accessibility of DNA for transcription. Alterations in histone modifications may lead to increased or decreased expression of genes involved in metabolism and fat deposition;
- **chromatin remodeling** – this process refers to structural changes in chromatin that allow access to various regions of DNA. Through chromatin remodeling, cells are able to respond more rapidly and efficiently to environmental changes, which may affect the development of metabolic disorders;
- **DNA methylation** – this involves the addition of a methyl group to cytosine nucleotides, which can lead to gene silencing. In the context of obesity, alterations in methylation may influence genes involved in the regulation of appetite, metabolism, and energy homeostasis [19].

Biopsychosocial factors play a significant role in the pathogenesis of obesity, often exerting a much greater influence than individual lifestyle choices. Excessive food intake may serve as a manifestation of emotional difficulties. Some individuals turn to food as a coping mechanism in response to challenging emotions such as stress, sadness, anxiety, or loneliness. This phenomenon, commonly referred to as "emotional eating," may represent an attempt to alleviate negative feelings or to obtain temporary relief. Individuals who struggle to express their emotions may unconsciously use food as a means of communicating their internal experiences [20].

Epidemiology of Obesity

Currently, obesity has become a serious global health problem. The increase in the number of individuals affected by obesity is alarming, and projections for the future indicate a continued escalation of this unfavorable trend. According to the World Health Organization (WHO), the global prevalence of obesity has tripled since 1975 [1, 21]. Numerical data indicate that as many as 1.9 billion people worldwide are overweight, and approximately 650 million suffer from obesity. Estimates presented by the WHO show that 39% of the global population over the age of 18 is overweight, while obesity was observed in 11% of adult men and 15% of adult women [22, 23]. Obesity emerged as a significant health concern during the COVID-19 pandemic. Numerous studies suggest that the pandemic influenced people's lifestyles, which may have contributed to weight gain. It should be noted that obesity affects individuals of all ages, including children and adolescents. According to Fink et al., the prevalence of obesity in Germany in 2017 was 16% [24]. Importantly, obesity also constitutes a serious public health issue in the United States (USA), particularly among adolescents. According to data from the Centers for Disease Control and Prevention (CDC), approximately 20–21% of American teenagers may be classified as obese, a condition associated with numerous health risks, including type 2 diabetes, cardiovascular diseases, as well as psychological and emotional problems [25, 26]. In the adult population in the USA, the prevalence of obesity is twice as high as that observed among adolescents, remaining at approximately 42% [27].

It should be noted that nearly 60% of adult Poles are affected by excessive body weight, and among individuals belonging to the highest risk group for obesity, the prevalence may reach as high as 85%. Obesity among older adults represents a particularly pressing issue. In Poland, according to available statistical data, this condition has become widespread, especially among individuals aged 60 to 79 years. Approximately 50% of individuals aged 60 to 70 years and about 33% of those aged 70 to 79 years suffer from obesity. These statistics reflect a serious health concern that necessitates focused attention not only from the healthcare system but also from families and the individuals affected themselves [22, 23]. According to the *European Nutrition and Health Report*, overweight and obesity are most prevalent in Greece. The issue of overweight is observed in over 50% of men and slightly less than 40% of women. Moreover, nearly 30% of men and approximately 40% of women in Greece are affected by obesity. Due to the high prevalence of both overweight and obesity, Greece ranks among the leading countries in this regard, whereas countries such as France, Sweden, Denmark, and Norway report significantly more favorable outcomes. In these countries, overweight affects, on average, 35–41% of men and 20–24% of women. It should be noted that the prevalence of obesity in these populations is limited to approximately 9% of men and 8% of women. This disparity may suggest differences in dietary culture, lifestyle patterns, and access to healthy food options and physical activity opportunities [27, 28].

Health Consequences of Obesity

Obesity constitutes a serious health condition that may lead to numerous chronic diseases, including metabolic disorders and cardiovascular pathologies. It is particularly important to emphasize that visceral obesity - characterized by excessive fat accumulation within the abdominal cavity - significantly contributes to the development of various ailments, such as coronary artery disease, heart failure, and stroke. Furthermore, obesity is frequently associated with dyslipidemia. Individuals affected by obesity often present with elevated levels of total cholesterol and low-density lipoprotein (LDL) fractions, accompanied by reduced levels of high-density lipoprotein (HDL). Such lipid abnormalities promote the formation of atherosclerotic plaques within blood vessels [29, 30]. Excess adipose tissue secretes pro-inflammatory cytokines and hormones, which may contribute to the development of insulin resistance and cause damage to vascular endothelium. Cytokines such as adiponectin, leptin, and resistin - produced by adipocytes - play a significant role in regulating metabolic processes and inflammatory responses in the body. Elevated leptin levels, commonly observed in individuals with obesity, are associated with an intensified inflammatory state and an increased risk of atherogenesis, a consequence of leptin's influence on the immune system and the stimulation of pro-inflammatory cytokine production. It is important to note that C-reactive protein (CRP), an acute-phase protein, increases in response to inflammation, and elevated concentrations of CRP are frequently observed in individuals with obesity, insulin resistance, and other metabolic disorders. CRP may interfere with insulin signaling, thereby contributing to the further deterioration of glucose metabolism [31]. Moreover, obesity may significantly affect female reproductive health, with obesity-related complications increasing the risk of infertility. A higher body mass index (BMI) is associated with a range of hormonal imbalances that may adversely affect the ovulatory cycle and fertility potential.

In women diagnosed with polycystic ovary syndrome (PCOS), obesity may exacerbate the symptoms of the condition and elevate the risk of developing insulin resistance [15, 16]. Current research has also demonstrated a link between obesity, diabetes, and various forms of cancer. Notably, hyperinsulinemia, chronic inflammation, and the pharmacological management of hyperglycemia constitute important factors in the understanding of metabolic diseases, particularly type 2 diabetes and obesity [31, 32, 33]. Studies have shown that overweight and obesity can lead to hormonal dysregulation within the body, which in turn may increase the risk of developing hormone-dependent malignancies, such as breast cancer, endometrial cancer, and ovarian cancer. Furthermore, academic literature also points to a correlation between obesity and the risk of colorectal, colon, and rectal cancers [34, 35].

Pharmacological Treatment of Obesity

The treatment of obesity and overweight requires a holistic approach encompassing both dietary habit modification and increased physical activity. In situations where these primary interventions fail to yield satisfactory outcomes within a period of 3 to 6 months, pharmacotherapy may be justified. It is essential to emphasize that the pharmacological management of obesity aims to support weight reduction in patients who have not achieved adequate results solely through lifestyle changes. The indications for the use of anti-obesity medications include patients with a body mass index (BMI) of 30 kg/m² or higher, as well as individuals with a BMI exceeding 27 kg/m² who present with comorbid conditions such as type 2 diabetes mellitus, arterial hypertension, or dyslipidemia [36].

Liraglutide

Liraglutide is a pharmacological agent used in the treatment of type 2 diabetes mellitus, acting as an analogue of the incretin hormone glucagon-like peptide-1 (GLP-1 (7-37)). Its mechanism of action involves the stimulation of insulin secretion in response to elevated blood glucose levels, alongside the inhibition of glucagon release, which in turn reduces hepatic gluconeogenesis and glycogenolysis. Additionally, liraglutide delays gastric emptying, thereby contributing to increased satiety and a reduction in appetite. This physiological effect is of particular importance in the context of weight loss, as it leads to decreased caloric intake, which may facilitate body weight reduction [37]. The action of liraglutide is not limited to the gastrointestinal system but also extends to the central nervous system, particularly to brain structures such as the hypothalamus. Within the arcuate nucleus of the hypothalamus, critical interactions occur between neurons that secrete orexigenic (appetite-stimulating) and anorexigenic (appetite-suppressing) substances. Liraglutide activates pro-opiomelanocortin (POMC) neurons, which exert anorexigenic effects, while simultaneously inhibiting the release of neuropeptide Y (NPY) and Agouti-related peptide (AgRP), thereby reducing the desire to eat and enhancing the sensation of fullness. Moreover, liraglutide influences the mesolimbic system, which is associated with the brain's reward circuitry and the hedonic aspects of food consumption. By modulating signals within this system, liraglutide may attenuate the reward response to food, thereby diminishing appetite and altering the individual's relationship with eating, ultimately supporting the weight reduction process [37, 38].

Liraglutide is administered once daily in the form of a subcutaneous injection [39]. Treatment typically begins with a dose of 0.6 mg per day. This standard initial approach is intended to minimize the risk of adverse effects, particularly nausea. Subject to patient tolerance, the dose is increased weekly until the maximum recommended daily dose of 3.0 mg is reached [37]. Liraglutide may induce adverse effects, primarily involving the gastrointestinal system, including nausea, diarrhea, vomiting, constipation, dyspepsia, abdominal pain, and gastric discomfort. The dosing regimen of liraglutide is of particular importance, as dose escalation is frequently associated with an intensification of side effects, especially during the early stages of therapy. Many patients experience these symptoms at the onset of treatment; however, they may subside over time as the body adapts to the medication. Importantly, according to current clinical guidelines, dose adjustment is not required in patients with impaired renal or hepatic function, which renders liraglutide a relatively safe pharmacological option for these populations. With regard to its effects on the cardiovascular system, it has been observed that liraglutide may cause an increase in heart rate. This phenomenon is associated with the presence of GLP-1 receptors in the sinoatrial node of the heart. Nevertheless, numerous clinical studies, including the LEADER trial, have demonstrated that the use of liraglutide is associated with a reduction in the risk of cardiovascular events, including cardiovascular-related mortality [38, 39].

Semaglutide

Semaglutide is a pharmaceutical agent used in the treatment of type 2 diabetes mellitus and obesity. Similar to liraglutide, it functions as a glucagon-like peptide-1 (GLP-1) analogue, exerting its therapeutic effects by stimulating insulin secretion, inhibiting glucagon release, and delaying gastric emptying. These mechanisms contribute to the reduction of blood glucose levels and the suppression of appetite. Structural differences between semaglutide and liraglutide are of critical importance for their pharmacodynamics and pharmacokinetics. Semaglutide possesses a modified molecular structure that enhances its stability and prolongs its duration of action. Specifically, the substitution of alanine with α-aminoisobutyric acid at position eight, the replacement of a C16 fatty acid with a C18 chain, and the attachment of the latter via a linker composed of glutamic acid and bis-aminoethoxyacetyl confer semaglutide with an extended half-life of approximately 160 hours. This prolonged duration enables once-weekly administration, offering greater convenience to patients compared to daily injections [40]. Semaglutide is available in two dosing options: 0.5 mg and 1.0 mg, allowing for individualized therapeutic adjustment. Its efficacy and favorable safety profile have rendered it a widely adopted option in the pharmacotherapy of both diabetes and obesity. Additionally, semaglutide is available in an oral tablet formulation. This form was developed by combining semaglutide with the sodium salt of salcaprozate (SNAC), which facilitates enhanced gastrointestinal absorption relative to the injectable form. It is essential for patients to be aware that the absorption of semaglutide may be significantly reduced if taken with food or large volumes of fluid. Therefore, it is recommended that oral semaglutide be administered on an empty stomach to ensure optimal absorption and therapeutic effectiveness [41].

Orlistat

Orlistat is a pharmacological agent used in the treatment of obesity, which acts through the inhibition of gastric and pancreatic lipases. Its mechanism of action involves covalent binding to the serine residue in the active site of these enzymes, resulting in the suppression of their enzymatic activity. Consequently, the hydrolysis of triglycerides is limited, leading to reduced absorption of monoglycerides and free fatty acids into the body. Clinical studies have demonstrated that orlistat can reduce dietary fat absorption by approximately 30%, thereby contributing to weight loss in patients undergoing treatment with this drug. Additionally, a beneficial effect of orlistat on the lipid profile has been observed, including a reduction in total cholesterol and low-density lipoprotein (LDL) cholesterol levels [42]. Importantly, the use of orlistat may be particularly effective in the management of overweight or obese individuals with concomitant dyslipidemia, and its efficacy may be enhanced when combined with a low-fat diet and physical activity. However, it must be noted that, like all medications, orlistat may cause side effects. The most common adverse reactions include diarrhea, abdominal pain, and oily stools. These symptoms are frequently the result of unabsorbed dietary fats, which is an intended pharmacological effect, although it may be bothersome for some patients. It is essential that patients with hepatic dysfunction exercise caution when using orlistat, as existing studies have indicated that its administration may contribute to the development of cholelithiasis and subacute hepatic failure. Orlistat, as a pharmacological agent used in the treatment of obesity, holds significant clinical relevance due to its interactions with other medications. It limits the absorption of numerous active substances, which may result in a reduction of their therapeutic efficacy. In particular, patients receiving medications such as amiodarone, cyclosporine, levothyroxine, and certain antiretroviral drugs should be monitored for potential changes in drug activity and effectiveness. Additionally, orlistat interferes with the absorption of fat-soluble vitamins, which may lead to deficiencies, especially of vitamin K. This is particularly relevant in patients undergoing treatment with warfarin, where such an interaction may necessitate adjustment of anticoagulant dosages [43].

Setmelanotide

Setmelanotide is a novel pharmacological agent that introduces new possibilities in the treatment of obesity, particularly in the context of its genetic origins. As an agonist of the melanocortin-4 receptor (MC4R), its primary function is to enhance the regulation of appetite and metabolism within the body. The use of setmelanotide is especially significant in patients with Bardet-Biedl syndrome, as well as in individuals with proopiomelanocortin (POMC) or leptin receptor (LEPR) deficiencies resulting from genetic mutations. The approval of this drug by the U.S. Food and Drug Administration (FDA) in 2020, and subsequently by the European Medicines Agency (EMA) in 2021, underscores its therapeutic potential and relevance in addressing obesity, which remains one of the most pressing public health concerns in modern societies. Setmelanotide may serve as an effective treatment option for patients who do not achieve success through conventional obesity therapies. Its primary mechanism of action involves the stimulation of the MC4R receptor, thereby restoring balance in the neuroendocrine pathways responsible for appetite and metabolic regulation. This effect results in the induction of satiety, ultimately contributing to body weight reduction.

In accordance with current recommendations, treatment with setmelanotide in patients over the age of 12 begins with a dose of 2 mg, administered once daily for a period of two weeks via subcutaneous injection [44]. In the event of adverse effects or poor tolerability, the dosage may be reduced to 1 mg per day. Conversely, if the medication is well tolerated, an increase to 3 mg per day may be considered. For children aged 6 to 12 years, it is recommended to initiate therapy with a dose of 1 mg per day for a period of two weeks [45]. Increased skin pigmentation is one of the known effects of the drug, as setmelanotide acts on melanocortins, which influence melanin production. Injection site reactions, such as hypersensitivity, are also typical for medications administered via subcutaneous injection. Among the commonly reported adverse effects are gastrointestinal disturbances, including nausea, vomiting, and diarrhea. Among the less frequent side effects, spontaneous penile erection has been observed in male patients [44, 45].

Naltrexone/Bupropion

The combination drug comprising naltrexone and bupropion, known as naltrexone/bupropion, is used in the treatment of obesity and acts on mechanisms related to appetite regulation and the reward system. Naltrexone, an opioid receptor antagonist, blocks opioid receptors, which may reduce hunger and food cravings. Bupropion, on the other hand, as a norepinephrine and dopamine reuptake inhibitor, affects neurotransmitters associated with mood and motivation, which may also support the weight loss process. The approval of this combination by the Food and Drug Administration (FDA) in 2014 and by the European Medicines Agency (EMA) in 2015 introduced new therapeutic possibilities for individuals with obesity who had previously attempted to lose weight but failed to achieve satisfactory outcomes [46]. Bupropion, by acting on neurons that secrete pro-opiomelanocortin (POMC) and the cocaine- and amphetamine-regulated transcript (CART) system, stimulates the sensation of satiety and increases energy expenditure. Naltrexone, as an opioid receptor antagonist, blocks the action of β-endorphins, which may inhibit POMC neuronal activity. In this manner, naltrexone enhances the effect of bupropion, leading to a further reduction in appetite and supporting the weight loss process [47]. This medication is available in tablet form. According to current guidelines, the patient should take naltrexone/bupropion for one week in the morning only. In the second week, the dosage increases to one tablet in the morning and one in the evening; in the third week, two tablets in the morning and one in the evening; and in the fourth week, two tablets in the morning and two in the evening. Adverse effects associated with this medication include headache, dizziness, dry mouth, vomiting, diarrhea, nausea, and constipation. Contraindications for the use of naltrexone and bupropion include arterial hypertension, seizures, abrupt alcohol withdrawal, anorexia nervosa, bulimia nervosa, and the use of benzodiazepines, barbiturates, or antiepileptic drugs. Patients undergoing treatment with this medication should also be closely monitored for symptoms of depression or suicidal ideation [46, 47].

Phentermine

Phentermine is a substance used in the treatment of obesity, acting on the nervous system, particularly by increasing the concentration of norepinephrine in the brain. It is classified as a noradrenergic and possibly dopaminergic sympathomimetic amine, which leads to elevated norepinephrine levels in the hypothalamus. This increase enhances the signaling of the pro-opiomelanocortin (POMC) neuronal pathway, resulting in the release of α-melanocyte-stimulating hormone (α-MSH), which binds to melanocortin-4 receptors. Phentermine exerts its effects by stimulating neuronal pathways that induce a sensation of satiety and reduce appetite. As a result, patients may find it easier to control their eating behaviors, thereby supporting the weight loss process [48]. Phentermine is most commonly employed as a short-term weight loss therapy, and its efficacy is particularly evident when combined with dietary modifications and increased physical activity. Due to its sympathomimetic action, it may cause certain adverse effects such as elevated blood pressure, tachycardia, insomnia, or dry mouth. Therefore, its use should be strictly supervised by a physician, and patients must be informed of the potential risks associated with the treatment. Phentermine is not intended for long-term use. According to current knowledge, the standard adult dose is up to 37.5 mg once daily, recommended before breakfast, with the possibility of individual dosage adjustment down to 9.375 mg. The expected reduction in body weight averages approximately 5% of the baseline body mass, although in certain cases it may exceed 10%. In studies utilizing an average daily dose of 27.5 mg over a period of approximately 13.2 weeks, a mean weight loss of 6.3 kg was observed. It is important to note, however, that the effectiveness of treatment may vary depending on individual patient factors, as well as adherence to dietary and physical activity recommendations [48].

Conclusions

Obesity is a serious health condition that often necessitates a comprehensive approach to treatment. Individuals affected by overweight or obesity may benefit from a variety of strategies aimed at halting the progression of the disease and improving overall health status. The cornerstone of obesity management remains the modification of dietary habits. In contemporary clinical practice, pharmacological treatment has become an increasingly important modality, offering support in appetite regulation or the inhibition of fat absorption. It is essential that individuals with obesity collaborate closely with physicians, dietitians, and other healthcare professionals to develop a personalized treatment plan tailored to their specific needs and capabilities. Lifestyle modifications should be introduced gradually and in a balanced manner to ensure sustainable, long-term outcomes. Modern anti-obesity agents such as liraglutide, semaglutide, and phentermine have demonstrated efficacy in promoting weight reduction. When combined with lifestyle interventions - such as dietary adjustments and increased physical activity - these medications may lead to a significant decrease in body mass index (BMI) among patients with overweight or obesity. It is crucial that pharmacological therapy be integrated as part of a multifaceted approach to obesity management, one that also encompasses psychological support and health education, in order to maximize therapeutic outcomes and promote lasting behavioral change.

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