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OBESITY AS A REFLECTION OF PSYCHO-EMOTIONAL DISORDERS: FOCUS ON PHARMACOTHERAPY

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Obesity is a vivid example of a multifactorial disease. In its development, not only the discrepancy between the energy intake and its expenditure but also various neurohumoral mechanisms, as well as external socio-economic and psychosocial factors, play important roles. One of the frequent options for combining psychoemotional disorders with obesity is the development of certain types of eating disorders in a patient. In this regard, the actual problem is to find the optimal therapeutic and prophylactic strategy in the management of such patients.

The aim of the work is to analyze the literature data on the features of the pathogenetic mechanisms of the obesity development against the background of psychoemotional disorders that are realized through eating disorders, and to identify the possibilities of using sibutramine to carry out a pharmacological correction of these pathological conditions.

Materials and methods. In the process of selecting materials for writing a review article, the following databases were uses: PubMed, Scopus, Web of Science, Google Scholar, ScienceDirect, etc. The search carried out, was based on the publications for the period from 2009 to 2020. The following words and phrases were chosen as parameters for the literature selection: obesity, psycho-emotional disorders, eating disorders, sibutramine.

Results. This review summarizes the main pathogenetic aspects that unite both the development of psychoemotional and metabolic disorders. A modern classification of obesity, taking into account the latest domestic and international recommendations of professional communities, is given. Eating disorders are considered in detail, their socio-psychological and psychiatric classifications are given. The prospect of choosing a therapeutic and prophylactic strategy for managing such patients is assessed, depending on the presence of psycho-emotional and eating disorders.

Conclusion. Thus, the combined drug containing sibutramine and metformin registered in the Russian Federation is effective, safe and can be used in patients with alimentary obesity and eating disorders, taking into account contraindications.

Keywords: obesity; psychoemotional disorders; eating disorders; sibutramine

Abbreviations: CNCD – chronic non-communicable diseases; RF – Russian Federation; WHO – World Health Organization; BMI – body mass index; WC – waist circumference; HC – hip circumference; CVD – cardiovascular diseases; NA – anorexia nervosa; BN – bulimia nervosa; PO – pathological overeating; GIT – gastrointestinal tract; AH – arterial hypertension; BP – blood pressure; DM2 – type 2 diabetes mellitus; CI – confidence interval.

ОЖИРЕНИЕ В ЗЕРКАЛЕ ПСИХОЭМОЦИОНАЛЬНЫХ НАРУШЕНИЙ: ФОКУС НА ФАРМАКОТЕРАПИЮ

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Ожирение представляет собой яркий пример многофакторного заболевания, в развитии которого важную роль играет не только несоответствие между поступлением и расходом энергии, но и различные нейрогуморальные механизмы, а также внешние социально-экономические и психосоциальные факторы. Одним из частых вариантов сочетания психоэмоциональных расстройств с ожирением является развитие у пациента тех или иных типов нарушений пищевого поведения. В связи с этим, актуальной проблемой является поиск оптимальной терапевтической и профилактической стратегии в ведении таких пациентов.

Цель. Проанализировать данные литературы об особенностях патогенетических механизмов развития ожирения на фоне психоэмоциональных расстройств, реализующихся посредством нарушений пищевого поведения, и обозначить возможности применения сибутрамина с целью фармакологической коррекции данных патологических состояний.

Материалы и методы. В процессе подбора материала для написания обзорной статьи использовали такие базы данных, как: PubMed, Scopus, Web of Science, Google Scholar, ScienceDirect, и др. Поиск осуществлялся по публикациям за период с 2009 по 2020 гг. Параметрами для отбора литературы были выбраны следующие слова и словосочетания: ожирение, психоэмоциональные нарушения, расстройства пищевого поведения, сибутрамин.

Результаты. В настоящем обзоре обобщаются основные патогенетические моменты, объединяющие как развитие психоэмоциональных, так и метаболических нарушений. Дается современная классификация ожирения, с учетом последних отечественных и международных рекомендаций профессиональных сообществ. Подробно рассматриваются нарушения пищевого поведения, дается их социально-психологическая и психиатрическая классификации. Оценивается перспектива выбора терапевтической и профилактической стратегии ведения таких пациентов в зависимости от наличия психоэмоциональных расстройств, нарушений и пищевого поведения.

Заключение. Таким образом, зарегистрированный в Российской Федерации комбинированный препарат, содержащий сибутрамин и метформин, представляет собой эффективное и безопасное лекарственное средство, которое может применяться у пациентов с алиментарным ожирением и нарушениями пищевого поведения при учете противопоказаний.

Ключевые слова: ожирение; психоэмоциональные нарушения; расстройства пищевого поведения; сибутрамин

Список сокращений: ХНИЗ – хронические неинфекционные заболевания; РФ – Российская Федерация; ВОЗ – Всемирная Организация Здравоохранения; ИМТ – индекс массы тела; ОТ – окружность талии; ОБ – окружность бедер; ССЗ – сердечно-сосудистые заболевания; НА – нервная анорексия; НБ – нервная булемия; ПП – патологическое переедание; ЖКТ – желудочно-кишечный тракт; АГ – артериальная гипертензия; АД – артериальное давление; СД2 – сахарный диабет 2 типа; ДИ – доверительный интервал.

INTRODUCTION

Modern development rates of high-tech types of medical care and the obvious progress in the field of pharmacology have made the long-standing dream of mankind to overcome many serious and incurable ailments possible. However, the further progress goes, the more obvious it becomes that some diseases, which have not been previously given much attention to, are now acquiring such threatening forms that they have begun an active offensive against humanity. Obesity, included in the international classification of diseases only in 1950, but spreading around the world at an incredible speed and carrying with it a huge amount of physical and psycho-emotional suffering for a person, can be attributed to such insidious pathologies [1].

Over the past decades, the number of diagnosed patients with obesity or overweight worldwide has increased severalfold. So, in 2016, already about 40% of the adult population was overweight, and 13% were obese[1]. According to experts, with continuing trends, by 2050, 45% of our planet population, will be overweight, and 16% will be obese [1]. According to the latest data, in 2019 obesity rose to the fifth place in the structure of risk factors for premature death worldwide, and the number of people who die annually from the consequences of obesity, is almost 3 million people [2].

Obesity is a significant risk factor for the development of the most common chronic non-communicable diseases (CNCD) in humans, such as cardiovascular, cerebrovascular, oncological, diabetes mellitus, pathologies of the respiratory system and the musculoskeletal system. In addition, the presence of obesity significantly affects the course and prognosis of a number of infectious diseases, including a new coronavirus infection. Thus, all of the above mentioned can lead to an increase in the burden on healthcare systems in all countries worldwide, and will require huge investments to prevent and overcome these consequences [2, 3].

In Russia, the prevalence of obesity in the new millennium was studied in the epidemiological research "ECVD-RF" (Epidemiology of Cardiovascular Diseases and their risk factors in the regions of the Russian Federation). According to the results, it amounted to 29.7%, which, in comparison with the data gained at the beginning of the nineties of the last century, turned out to be several times higher. The researchers also notified that woman over 45 are more likely to be obese in Russia, and overweight is associated with a high socioeconomic status [4].

Thus, in the Russian Federation, as well as throughout the world, the situation with obesity has ceased to be a background problem and is increasingly coming to the fore in the study of topical issues of treatment and prevention of the most common CNCDs, that occupy a leading position in the incidence and mortality of the population [5].

[1] World Health Organization. Obesity and overweight. Available from: https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight.

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THE AIM of the work is to analyze the literature data on the features of the pathogenetic mechanisms of the obesity development against the background of psychoemotional disorders that are realized through eating disorders, and to identify the possibilities of using sibutramine to carry out a pharmacological correction of these pathological conditions.

MATERIALS AND METHODS

In the process of selecting materials for writing a review article, the following databases were uses: PubMed, Scopus, Web of Science, Google Scholar, ScienceDirect, etc. The search carried out, was based on the publications for the period from 2009 to 2020. The following words and phrases were chosen as parameters for the literature selection: obesity, psycho-emotional disorders, eating disorders, sibutramine.

RESULTS AND DISCUSSION

Definition and classification

According to the definition of the World Health Organization (WHO), obesity is an abnormal or excessive fat accumulation in the body, which can lead to adverse consequences for human health[2]. In the latest version of clinical guidelines for the diagnosis and treatment of patients with obesity, the Association of Endocrinologists of the Russian Federation provides a more complete definition of this pathology. Obesity is a chronic disease characterized by excessive accumulation of adipose tissue in the body, which poses a threat to health and is a major risk factor for several other chronic diseases, including type 2 diabetes mellitus (DM2) and cardiovascular diseases [6].

For a long time, the only indicator that the doctor was guided by when diagnosing overweight or obesity, was the body mass index (BMI). BMI is calculated as the ratio of body weight in kilograms to the square of height in meters (kg/m^2). At the same time, according to the opinion of WHO experts[3], overweight is established if the BMI is greater than or equal to 25, and obesity – if the BMI is greater than or equal to 30, and then the degree of obesity is specified (Table 1). However, despite the apparent convenience and ease of the BMI indicator use, it is currently only considered an indirect criterion, since it has certain limitations for use in children, the elderly, athletes and pregnant women. It may also correspond to a different degree of developing complications risk, which was the reason for revising this classification and creating a new one (Table 2) [6, 7].

Considering that the main morphological substrate of adverse cardio- and metabolic obesity risks is associated with an excessive accumulation of visceral adipose tissue, current domestic and international clinical recommendations of professional communities of endocrinologists, cardiologists, internists, bariatric surgeons, etc. emphasize the need to measure, along with BMI, waist circumference (WC) and the ratio of WC to hip circumference (HC). Thus, the obesity phenotype, and hence a lot of risks associated with it, can be assessed [6–10]. So WC ≥ 94 cm in men and ≥ 80 cm in women is a diagnostic criterion for visceral obesity, and the WC/HC ratio > 0.9 in men and > 0.85 in women is a metabolically unhealthy obesity phenotype, regardless of the BMI value [8, 9].

According to the etiological principle, obesity is classified into primary (exogenous-constitutional or alimentary) and secondary (symptomatic, associated with other diseases or conditions) [6]. Thus, the secondary type of obesity includes obesity as a part of known genetic syndromes; cerebral obesity (due to the brain damage); obesity due to other diseases of the endocrine system; obesity against the background of taking drugs that contribute to weight gain. However, the most common etiological type of obesity today is primary alimentary or exogenous-constitutional obesity. Thus, the issues of pathogenesis, or causes of overnutrition in most obese patients, become very relevant, given the possibility of developing effective methods of prevention and treatment.

Obesity and psycho-emotional disorders

According to modern concepts, obesity is a vivid example of a multifactorial disease, in the development of which an important role is played not only by the discrepancy between the energy intake and its expenditure, but also by various neurohumoral mechanisms, as well as by external socio-economic and psychosocial factors [11, 12].

It should be notified that the increase in the prevalence of obesity over the past decades may be closely related to the growth rate of the prevalence of mental health disorders, especially the affective spectrum (depression and anxiety disorders), among the population of many developed countries [13, 16]. "The Global Burden of Diseases, Injuries, and Risk Factors Study", conducted in 2017, demonstrated an increase in the prevalence of affective disorders worldwide, which are among the top three causes of disability in both men and women [14]. In the Russian Federation, the prevalence of affective disorders among the general population is as follows: depression comprises 8.8% and anxiety disorders – 18.1%. Among the patients with CNCDs seeking for medical care in outpatient and inpatient health care facilities, they are almost 50% [15, 16]. The conducted studies and meta-analyses have shown that affective violations increase the risk of developing both the CNCDs themselves (especially CVDs) and unfavorable cardiovascular outcomes [17–24]. At the same time, pathogenetic dysfunction of monoaminergic systems, mainly serotonin-, norepinephrine- and dopaminergic ones, in the central nervous system underlies the development of both affective disorders (depression and anxiety disorders) and obesity [25]. It is known that serotonin regulates the rate of satiety development, affects appetite and the choice of nutrients, suppresses the desire to overeat foods rich in carbohydrates and fats, and

[2] Ibid.
[3] Ibid.

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its deficiency in depression, on the contrary, increases craving for such food sources, the intake of which not only reduces the vegetative symptoms of depression but also promotes weight gain. Norepinephrine is also involved in the regulation of food intake, hereby, it influences neuropeptide Y and leptin levels, and the stimulation of dopamine receptors is accompanied not only by a decrease in the volume and number of meals, but it also regulates the energy consumption [26]. It should be notified that the severity of affective disorders also correlates with the severity of obesity and comorbid CVDs [27–29]. However, in real clinical practice, internists (therapists, endocrinologists, cardiologists, etc.) tend to overlook such relationships due to insufficient awareness of the pathogenetic mechanisms and risks associated with mental health [30, 31].

Another option for combining psycho-emotional disorders with obesity is the development of certain variants of eating disorders in the patient. It is known that the majority of obese patients are not aware of the presence of any disorders associated with eating, explaining the excess in nutrition by addiction to tasty and favorite dishes or products. However, at the same time, in most obese patients, difficulties gradually begin to arise with an independent cessation of food intake, the control over the amount of food eaten gets lost, the feeling of fullness disappears or lags, contributing to constant overeating. Thus, a daily consumption of excess calorie food, with gradually increasing portion sizes and the formation of circadian eating disorders is often accompanied by chronic psycho-emotional stresses and physical inactivity. These factors contribute to the rapid progression of obesity, most fully illustrating undiagnosed eating disorders. It should be emphasized that the comorbidity of eating disorders with depressive or anxiety disorders can develop long before the formation of clinically significant obesity [32–34].

The response to various stresses that accompany human life in abundance in the modern world is one of the important causes of obesity, which is realized through the development of eating disorders. Often, the beginning of the formation of eating disorders is preceded by a traumatic situation, accompanied by the development of an affective disorder of the anxiety or depressive spectrum. Next, the hyperphagic reaction joins, i.e. overeating, as a form of relieving a psycho-emotional stress, which is a simplified behavioral response that gives an imaginary feeling of protection and calm. This is how a stereotyped compensatory response to situations of psycho-emotional stress is launched and consolidated by overeating, which gives only a short-term relief. However, in the future, due to excess weight gain, patients begin to develop secondary depressive or anxiety disorders associated with a negative perception of their appearance and feelings about their helplessness in controlling food intake [35]. Psychoemotional tension or stress can contribute to the development of primary obesity not only due to hyperphagic reactions and poor nutrition, but also by increasing the risk of alcohol abuse and enhancing the effects of physical inactivity. There is also a relationship between the severity of depressive disorders, the severity of eating disorders and the progression of obesity [35, 36]. In the studies by E.M. Pisetsky et al., it was shown that eating disorders can further increase the risk of suicide attempts, including the situations after the relief of the main depression symptoms [37]. Due to this close relationship, eating and psycho-emotional disorders, on the one hand, contribute to weight gain, and on the other hand, progression of obesity worsens the mood and psycho-emotional state of a person, strengthening and perpetuating eating disorders [38].

Table 1 – Classification of obesity by BMI[4]

Body mass	BMI, kg/m^2	Risk of concomitant diseases
Underweight	<18.5	Low (increased risk of other diseases)
Normal body weight	18.5–24.9	Usual
Overweight	25.0–29.9	Higher
Obesity I degree	30.0–34.9	High
Obesity II degree	35.0–39.9	Very high
Obesity III degree	≥40	Extremely high

Table 2 – Classification of obesity by stages

Diagnosis	Anthropometric data	Clinical data
Overweight	BMI ≥ 25.0–29.9 kg/m^2	No complications associated with obesity
Obesity stage 0	BMI ≥ 30.0 kg/m^2	No complications associated with obesity
Obesity stage 1	BMI ≥ 25.0 kg/m^2	One or more moderate complications associated with obesity
Obesity stage 2	BMI ≥ 25.0 kg/m^2	One or more severe obesity-related complications

Note: the presence or absence of concomitant diseases, the course of which is directly associated with obesity (i. e., DM2, arterial hypertension, non-alcoholic fatty liver disease, etc.), their severity determines the stage of obesity and, accordingly, the choice of therapy.

[4] Ibid.

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Table 3 – Summary of data from studies on the use of drugs containing sibutramine and sibutramine in combination with metformin

Sl. No.	Detected connection	Sample	Referent	Research results	Reference
1.	Sibutramine therapy is associated with a reduced risk of cardiovascular complications in patients without contraindications	Obese adults N=23,927	Orlistat N=77047	Against the background of orlistat therapy, the risk of myocardial infarction or cerebrovascular accident HR – 1.69, at p=95%, CI 1.12–2.56. Against the background of sibutramine therapy, the risk of myocardial infarction or cerebrovascular accidents HR – 1.52, p=95%, CI 0.92–2.48.	[49]
2.	Therapy with sibutramine (Reduxin®) for 12 months is associated with persistent and clinically significant weight loss and WC, regardless of gender, age and the presence of concomitant diseases	Adult patients with obesity and without comorbid pathology, N=98,774	–	For 12 months of therapy: a clinically significant decrease in body weight by 10-20%, 20% or more in 52.1% and 42.1% of patients, respectively. The mean reduction in waist circumference over 3, 6, and 12 months of therapy was 6.3±4.31 cm, 10.6±6.30 cm, and 16.0±8.94 cm, respectively (p<0.001).	[50]
3.	Weight loss during therapy with the combined drug sibutramine + metformin is associated with the achievement of metabolic health compensation parameters, improved prognosis and quality of patients' lives	Adult patients with obesity and disorders of carbohydrate metabolism, N=55	–	For 6 months of therapy, a decrease in body weight by 10% or more – in 91% of patients; a decrease in TG levels by 0.73±1.0 mmol/l (25%); total cholesterol (TC) – by –0.97±4.8 mmol/l (17%); LDL – by –0.67±1.0 mmol/l (20%) and an increase in HDL by 0.24±43.8 mmol/l (16%) from the initial level; a decrease in FFA from 0.54±0.28 to 0.43±0.25 meq/l, by 20.3% (p<0.001). Achievement of normal values of glycemic parameters observed in 93.2% of patients	[45]
4.	Adding a combination of sibutramine and metformin to the base hypoglycemic therapy in patients with type 2 diabetes and obesity provides effective and safe weight loss, and also improves the effectiveness of treatment, including reaching the target values of carbohydrate and lipid metabolism	Adult patients with obesity and type 2 diabetes, N= 5812	–	A decrease in BMI for 3 and 6 – 3.4±1.5 kg/m^2 (on average 9.5±4.2 kg) and 5.4±2.3 kg/m^2 (15.1±6.4 kg), respectively. The average change in glucose level: –2.0±1.6 mmol/l, the average change in the level of glycated hemoglobin was –1.2±1.1%.	[47]
5.	Therapy with the combined drug sibutramine + metformin (Reduxin® Forte) for 12 months was accompanied by a decrease in body weight, lipotoxicity, normalization of carbohydrate and lipid metabolism, a decrease in the level of leptin and postprandial ghrelin, and normalization of eating habits.	Adult patients with obesity and disorders of carbohydrate metabolism, N=78	–	Weight loss – 21.0±4.62 kg; a reduction in waist circumference – 16.8±3.2 cm; a decrease in TG levels by 0.43±0.3 mmol/l (14%); total cholesterol – by 0.78±0.67 mmol/l (13%); LDL – by 0.61±0.5 mmol/l (19.6%) and an increase in HDL by 0.15±0.2 mmol/l (14%), a decrease in fasting blood glucose by 0.82±0.6 mmol/l (13.1%) (p<0.001); a decrease in glycated hemoglobin – 0.42±0.05% (p<0.001); achievement of normal values of glycemia parameters – 99.3%; improving the quality of patients' lives.	[48]

Thus, obesity is formed as a result of complex pathogenetic and clinical interactions between psychoemotional and metabolic disorders. Due to all the reasons mentioned above, a detailed study of the eating disorders phenomenon, the mechanisms of its formation and consolidation, can help in choosing the most effective tactics for the treatment and prevention of weight gain in most patients with obesity.

Eating disorder

The interpretation of the term "eating disorder" from the standpoint of a psychiatrist and an endocrinologist or a psychologist is somewhat different. So, within the framework of socio-psychological typology, which is used in the practice of endocrinologists and nutritionists, as well as psychologists, eating disorders are understood as the use of such an amount of nutrients that does not correspond to the energy needs of the body. In modern society, unfortunately, eating disorders are considered as a socially acceptable variant of addictive behavior, in contrast to drug addiction, alcoholism or cigarette smo-

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king[5]. The essence of addictive or dependent behavior is the desire to escape from reality, artificially change one's psycho-emotional state, which gives the illusion of security and tranquility. Therefore, psychological personality traits, primarily pronounced personal anxiety, impulsivity, low self-esteem, and some psycho-emotional infantilism, are essential for the formation of obesity [34].

There are three main types of addictive eating behavior: external, emotional, restrictive [35]. The external type refers to eating that is not caused by hunger or low blood glucose, but by external causes. Such reasons include tasty-smelling and appetizing-looking dishes, a well-laid table, and the appearance of people eating, various advertising posters or videos with food. Accepting an invitation to "have a bite for company's sake", a hearty meal at a party or at a festive table; buying a large amount of food in a supermarket are also in the area of the responsibility of external eating behavior. From the situations that contribute to overeating with this type of eating behavior, internal causes become apparent and prompt, often in the field of interpersonal communication, when eating is associated with a means of establishing trusting relationships and encouragement. The external type of eating behavior gradually contributes to the formation of increased appetite and delayed satiety, which is often felt by such patients as mechanical fullness in the stomach or "abdominal discomfort" from overeating [35].

For the emotional type of eating behavior, as the term itself makes it clear, the reason for eating is not hunger either, but emotions make that person "comfort eat", calming himself in this way. The main triggers for emotional overeating can be a severe stress, fear, longing, anxiety, grief, feelings of loneliness and even boredom. As in the mechanism of the formation of affective disorders, with emotional eating behavior, an important role is played by the innate imbalance of neurotransmitter monoamines, which a person seeks to compensate for with a plentiful meal. A similar formation mechanism is also characteristic of other variants of addictive behavior, such as drug or alcohol addiction. Therefore, this type of eating behavior is also called "food drunkenness" [35, 38].

Restrictive eating behavior is characterized by adherence to meaningless and excessive dietary restrictions. Compliance with strict diets is accompanied by a strong feeling of hunger; it is replaced by a breakdown and overeating, the development of "dietary depression", which leads to the formation of a vicious circle. It must be emphasized that in most cases, combinations of different types of eating disorders can be identified in one patient at different times. Therefore, for example, a transition from an external or restrictive to an emotional type of eating disorder is possible against the background of a prolonged exposure to stressful factors. The degree of obesity does not correlate with the type of eating behavior [12, 36].

It should be emphasized that without establishing the type of eating disorder, it is impossible to build an effective treatment strategy and achieve long-term results. It is also important to know that in approximately 30% of patients, eating disorders first occur against the background of irrational diets, which lead to the development of emotional discomfort and cause them to refuse therapy. In addition, already existing disorders can be exacerbated by diet therapy [6, 12].

On the other hand, the practice of psychiatrists also uses its own classification of eating disorders, in accordance with the new International Classification of Diseases, 11th revision (ICD-11)[6]. According to this manual, eating disorders and eating behaviors are included in section L1-6B8. However, only eating disorders include abnormal eating behavior accompanied by marked concerns about weight and body shape. These conditions include anorexia nervosa (6B80), bulimia nervosa (6B81), binge eating (6B82), and a pathological preferential-restrictive eating disorder (6B83). However, it should be emphasized that not all of these conditions are associated with obesity[7].

Anorexia nervosa (AN) is clinically characterized by a gradual decrease in body weight to a degree that does not correspond to normative values, which cannot be explained by another health disorder and is not associated with the inaccessibility of food. Patients with AN intentionally prevent the recovery and maintenance of their normal body weight through persistent restriction of food intake or cleansing behavior (vomiting, use of laxatives and diuretics), as well as through excessive physical exertion. Low weight or body shape is central to self-assessment in the AN patients, and normal weight is mistakenly perceived as being overweight[8].

Bulimia nervosa (BN) is characterized by recurrent episodes of uncontrollable food consumption. At the moment of such overeating, a patient completely loses control over his eating behavior, eats noticeably more than usual and cannot stop eating or limit the amount of food eaten. Further, compensatory behaviors aimed at preventing weight gain develop – inducing vomiting, using laxatives and intense sports. Patients with (BN) are preoccupied with their weight and figure, which have a strong effect on their self-esteem[9].

Binge eating (BE) is also characterized by frequent episodes of uncontrollable food consumption, but unlike BN, bouts of overeating are not necessarily followed by compensatory behavior. However, these attacks are experienced as very unpleasant and are often accompanied by negative emotions such as feelings of guilt or disgust.

[5] Malkina-Pykh IG. Terapiya pishchevogo povedeniya [Eating behavior therapy]. Psychology. M.: Eksmo; 2007:1040 p. Russian

[6] ICD-11. Chapter 06 Statistical classification. M.: "KDU", "University Book", 2021. – 432 p. Russian

[7] Ibid.

[8] Ibid.

[9] Ibid.

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Pathological preferential-restrictive eating disorder is characterized by avoidance or restriction of food intake, which can lead to significant weight loss, clinically significant nutritional deficiencies up to the need for increased supplementation or tube feeding. This type of eating behavior, unlike AN, is not dictated by preoccupation with weight and figure. It is important to note that for the diagnosis of most of the listed mental disorders, an important requirement is the presence of severe distress, i.e. painful experiences, anxiety, discomfort due to a mental or behavioral deviation, and impaired functioning in one or more significant areas of life (personal, family, social, educational, professional, etc.).

Thus, in the clinical practice of internists, there may be patients with mental eating disorders, however, the severity of the clinical picture and the characteristic patterns of behavior of such patients should attract the attention of the attending physician and serve as a reason for referral to a psychiatrist.

Therapeutic strategies

Traditional approaches in the treatment of obesity are establishing a trusting relationship with the patient and discussing a realistic goal of weight loss; long-term and gradual changes in nutrition and the rejection of starvation diets; increasing and intensifying daily physical activities. It is optimal to make up an individual nutrition and training plan together with qualified specialists – a nutritionist and a physiotherapist, followed by a constant support for a long time [10, 11].

Recognizing the obviousness of any intervention aimed at reducing excess weight and maintaining optimal weight, cannot be considered as a one-time or short-term therapeutic intervention, the formation of proper eating behavior is important. Given the frequency of obesity comorbidity with a variety of psychoemotional disorders that have a mutually aggravating effect and prevent constant adherence to recommendations for lifestyle changes and nutrition, some patients require a consultation with a psychologist, psychotherapist or psychiatrist to select psychopharmacotherapy [10].

Prescribing drugs for the treatment of obesity is recommended for patients with a BMI ≥ 30 kg/m^2 (or a BMI ≥27 kg/m^2 in the presence of comorbid cardio-metabolic diseases) when they cannot achieve weight loss of 5–10% within 6 months against the background of the use of all non-drug methods or at the stage of maintaining the achieved result [6, 7, 10]. Currently, the following drugs for the treatment of obesity are registered in the Russian Federation: orlistat, liraglutide, sibutramine, including sibutramine + microcrystalline cellulose and sibutramine + metformin in the form of combinations. Each of the presented drugs has been briefly characterized in the light of solving the problem of eating disorders in obese patients.

Being an inhibitor of gastrointestinal lipase and having a therapeutic effect only within the gastrointestinal tract (GIT), orlistat prevents the splitting and subsequent absorption of fats and fat-soluble vitamins from food. Direct consequences of the mechanism of the orlistat action are such frequent side effects as fatty stools, oily discharge from the rectum, imperative urges to defecate, increased defecation and fecal incontinence, abdominal pains, gas with some amount of discharge from the intestine. These factors make the use of this drug somewhat difficult in the patients with eating disorders who cannot completely refuse fatty foods [6, 10]. The drug orlistat has also such registered contraindications as acute pancreatitis and the diseases accompanied by diarrhea; chronic malabsorption syndrome and cholestasis (since orlistat increases the likelihood of gallstone formation, leading to a decrease in gallbladder motility). It should be emphasized that the therapeutic effect of this drug is modest, and currently, there are no positive data to judge the effect of orlistat on the overall mortality or mortality from CVDs [10].

Liraglutide is an analog of human glucagon-like peptide-1. For a long time, being a hypoglycemic agent, it has been used only in the treatment of type 2 diabetes mellitus. The mechanism of liraglutide action is due to the reinforced feeling of stomach fullness and satiety, without increasing a 24-hour energy expenditure. It has been shown that liraglutide has a positive effect on cardiometabolic risk factors against the background of weight loss [11]. However, just as with orlistat, its side effects are direct acting and the most common are nausea, vomiting, diarrhea, constipation, dry mouth, dyspepsia, gastritis, gastroesophageal reflux, upper abdominal pains, bloating, belching, and cholelithiasis. The drug has also strict contraindications: with a history of medullary thyroid cancer, including family members; with the syndrome of multiple endocrine neoplasia type II; depression; suicidal thoughts or suicidal behavior, incl. in history, severe renal and hepatic insufficiency; chronic heart failure of the 4th functional class; to patients aged ≥75 years. Its use is not recommended to patients with inflammatory bowel disease and diabetic gastric paresis, it is recommended to take the drug in patients with mild to moderate hepatic insufficiency, thyroid disease and a history of acute pancreatitis with caution [10]. Thus, in addition to the impact on the quality of patients' lives due to the frequency of side effects, it has a wide range of contraindications. Liraglutide has an unfavorable effect associated with a possible negative effect on the psycho-emotional status of a person, which makes it impossible to recommend it as a drug of choice for the treatment of obesity to most patients [39].

In our country, sibutramine is the only currently registered drug for the treatment of obesity that has a central effect, being an inhibitor of the reuptake of serotonin, norepinephrine and, to a lesser extent, dopamine in the synapses of the central nervous system. Sibutramine has a dual mechanism of action: on the one hand, it accelerates the onset of satiety, significantly reducing

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the intake of calories from food; on the other hand, it increases the energy consumption of the body due to the activation of thermogenesis. As a whole, they lead to a more effective weight loss, regardless of gender, age, and the presence of concomitant diseases [40]. Moreover, it has been notified that the higher the initial BMI is, the more intense the decrease in body weight will be [41].

It should be notified that sibutramine therapy is accompanied by a feeling of "energy boost" and improved mood, which makes it easier to endure any food restrictions in the process of choosing the right diet [40]. It has also been shown that sibutramine not only provides effective weight loss, but also improves cardio-metabolic parameters. Thus, against the background of sibutramine therapy, the state of atherogenic dyslipidemia and the insulin resistance significantly improves (the levels of glycated hemoglobin, uric acid, triglycerides, total cholesterol, low-density lipoproteins decrease, and the content of anti-atherogenic high-density lipids increases) [41].

It should be notified that due to the sympathetic activation against the background of sibutramine therapy, a slight change in hemodynamic parameters is possible. Therefore, all patients need to control the pulse and blood pressure (BP) levels before starting therapy, then from the 1st to the 3rd month – once every 2 weeks; from the 4th to the 6th month – once a month; from the 6th to the 12th month – once every 3 months. The drug cannot be prescribed to the patients with uncontrolled arterial hypertension, i.e. if the blood pressure is constantly above 145/90 mm Hg, coronary heart disease, decompensated chronic heart failure, cardiac arrhythmias, previous cerebrovascular diseases (stroke, transient cerebrovascular accident), occlusive diseases of peripheral arteries in patients over the age of 65 years. However, in real clinical practice, in patients with obesity and controlled hypertension, sibutramine has shown itself to be an effective and safe drug that effectively reduces body weight [42]. The side effects such as loss of appetite, dry mouth, some agitation and an increased activity, sweating are usually mild, notified only at the beginning of treatment, are transient and, as a rule, do not require discontinuation of therapy. The use of sibutramine in combination with metformin increases the therapeutic efficacy of both components, both in patients with and without carbohydrate metabolism disorders [43].

Over the past decades, much experience has been gained in the clinical use of sibutramine and metformin used for treatment of obese patients. The expediency of combination therapy using sibutramine and metformin, and later the creation of a combination and its fixed form (Reduxin® Forte), was dictated by the need to obtain a more pronounced therapeutic effect through the active influence on various links in the obesity pathogenesis. In the international study that took place in medical centers in England, Canada, France and Belgium, the effect of sibutramine on body weight, metabolic control and blood pressure, was evaluated in obese patients treated with metformin and suffering from type 2 diabetes. The study included 195 patients (44% men) with DM2 and BMI >27 kg/m^2. The improvement in glycemic control in patients has been shown to occur in parallel with weight loss. The researchers concluded that sibutramine is an effective adjunct to the treatment of patients with obesity and T2DM with metformin [44].

According to Russian researchers, therapy with Reduxin® Forte for 24 weeks was also accompanied by significant changes in anthropometric parameters, i.e.: weight loss by 5% or more in 6 months of therapy was achieved in 94% of patients, while 91% of patients managed to reduce weight by 10% or more. Given the severity of weight loss, which was accompanied by a significant decrease in waist circumference, conclusions, regarding the effectiveness of the fixed combination (metformin + sibutramine) for weight loss, as well as the reduction of visceral fat, which helps to reduce the risk of complications, were drawn by A.S. Ametov et al. [45].

It has also been shown that the combined use of sibutramine with metformin not only increases the effectiveness of weight loss, but also reduces the level of chronic inflammation and the risk of complications associated with overweight, including CVDs and T2DM, in combination with a comprehensive restoration of metabolic health. These data are especially relevant in the context of reducing cardiovascular risks and improving the prognosis of such patients [46].

An analysis of the AURORA program results, which included a sample of 5812 patients taking a combination drug containing sibutramine and metformin, demonstrated clinically significant weight loss and a decrease in waist circumference in more than 90% of patients with T2DM, regardless of the underlying hypoglycemic therapy. In addition, the combination of sibutramine and metformin has been shown to have a positive effect on carbohydrate and lipid metabolism, contributing to an additional decrease in glycated hemoglobin and normalization of the atherogenic index in more than 50% of patients. It should be emphasized that the incidence of adverse events did not exceed 5.1%. All of the above mentioned, makes it possible to draw conclusions about the clinical feasibility of including combination therapy (sibutramine + metformin) in the therapy of patients with DM2 and obesity, since its use is effective and safe, regardless of the presence of polymorbid pathology and the use of various concomitant drugs [47].

In another study based on using a fixed combination of metformin + sibutramine, it was found out that during 12 months of therapy, the insulin resistance index normalized in 100% of patients. The dynamics of the decrease in BMI for 3 months of therapy was 3.6±1.1 kg/m^2 (at an average of 9.8±4.2 kg); for 6 months – 5.5±2.6 kg/m^2 (15.9±5.4 kg); for 2 months – 7.1±3.02 kg/m^2 (21.0±4.62 kg)

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(p<0.001). The decrease in WC for 3, 6 and 12 months of therapy, on average, amounted to 7.3±2.8, 13.1±6.4 and 16.8±3.2 cm, respectively, which indicates the advisability of taking the combination drug metformin + sibutramine to reduce the amount of visceral fat and reduce the risk of complications such as type 2 diabetes and CVD.

It is important to notify that during the therapy, a correction of the patients' eating behavior was observed: the ongoing treatment reduced the number of patients with the emotiogenic type of pathological overeating by 4.7 times, by 5.8 times with the external type, and by 1.9 times with the restrictive PO. At the end of taking the drug, 75.7% of patients observed a rational type and developed correct eating habits. The decrease in caloric intake during ad libitum food intake for 3 months of therapy was 36% (1648±852 kcal). Most patients notified a decrease in the frequency of unplanned meals, the disappearance of the need for evening meals. Approximately 89% of patients managed to achieve and maintain individual target values of daily caloric intake during the year of therapy [48].

Thus, taking into account the favorable cardio-metabolic profile of the therapeutic metformin action [49], which has been used for a long time in the treatment and prevention of all obesity-associated diseases, as well as its concomitant effects with sibutramine, one can be confident in the positive synergy of the double combination – sibutramine + metformin (Reduxin® Forte[10]). This makes it possible to achieve a significant reduction in body weight, compensation for metabolic disorders and correction of the eating habits of patients with obesity, which is the key to successful obesity therapy.

So, in October 2021, the Ministry of Health of the Russian Federation decided to amend the instructions for use of the drug Reduxin® Forte. Now, in addition to use in people with obesity, prediabetes and additional risk factors for developing DM2, the drug is also indicated for all patients with alimentary obesity (BMI ≥ 30) who do not have contraindications. This drug gives hope for the improvement in the situation with the treatment of obesity in most patients in our country. The summarized data from the studies of the efficacy and safety of the drugs containing sibutramine and its combination with metformin in routine clinical practice are presented in Table 3. It is interesting to conduct further studies to identify additional pleiotropic effects of this combination in obese patients.

CONCLUSION

Thus, the combined prevalence of obesity and psycho-emotional disorders worldwide is steadily increasing. Given the negative impact of eating disorders on the ability to effectively reduce and maintain optimal body weight, an earlier prescription of drug therapy that can affect both conditions is necessary. The combined drug containing sibutramine and metformin (Reduxin® Forte) registered in the Russian Federation is an effective and safe drug that can be used in all patients with alimentary obesity, taking into account contraindications.

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CONFLICT OF INTERESTS

The author declares no conflict of interest.

AUTHOR'S CONTRIBUTION

Veronika N. Shishkova – design development, material recruitment, analysis and interpretation of the results, writing and editing the text.

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