Pharmacological Strategies for Appetite Modulation in Eating Disorders: A Narrative Review

Фармакологические стратегии модуляции аппетита при расстройствах пищевого поведения: нарративный обзор литературы

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Review

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ABSTRACT

BACKGROUND: A substantial increase in the prevalence of eating disorders has been noticed over the past decades. Priority in the treatment of eating disorders is justifiably given to psychosocial interventions. However, it is also well known that centrally acting drugs can significantly affect appetite and food consumption.

AIM: To narratively review the available neurobiological data on the mechanisms of central regulation of eating behavior as a rationale to summarize pharmacological strategies for appetite modulation in eating disorders.

METHODS: The authors have carried out a narrative review of scientific papers published from January 2013 to March 2023 in the PubMed and Web of Science electronic databases. Studies were considered eligible if they included data on the neurobiological mechanisms of appetite regulation or the results of clinical trials of centrally acting drugs in eating disorders. Relevant studies were included regardless of their design. Descriptive analysis was used to summarize the obtained data.

RESULTS: The review included 51 studies. The available neurobiological and clinical data allowed us to identify the following pharmacological strategies for appetite modulation in eating disorders: serotonergic, catecholaminergic, amino acidergic and peptidergic. However, implementation of these data into clinical practice difficult due to an insufficient number of good-quality studies, which is particularly relevant for adolescents as there is a research gap in this population.

CONCLUSION: The progress in neurobiological understanding of the mechanisms of central regulation of appetite opens opportunities for new pharmacotherapeutic approaches aimed at changing the patterns of eating behavior. Obviously, treatment of eating disorders is a much broader problem and cannot be reduced to the correction of eating patterns. Nevertheless, at certain stages of treatment, drug-induced modulation of appetite can play an important role among multi-targeted biological and psychosocial interventions. Translation of neurobiological data into clinical practice requires a large number of clinical studies to confirm the long-term efficacy and safety of pharmacotherapeutic approaches and to develop personalized algorithms for the treatment of various forms of eating disorders in different age groups.

АННОТАЦИЯ

ВВЕДЕНИЕ: На протяжении последних десятилетий наблюдается значительный рост частоты расстройств пищевого поведения. При лечении расстройств пищевого поведения приоритет обоснованно отдается психосоциальным интервенциям. Вместе с тем хорошо известно, что лекарственные препараты центрального действия способны оказывать существенное влияние на аппетит и потребление пищи.

ЦЕЛЬ: Проанализировать и обобщить имеющиеся нейробиологические данные о механизмах центральной регуляции пищевого поведения для обоснования фармакологических стратегий модуляции аппетита при расстройствах пищевого поведения.

МЕТОДЫ: Авторами выполнен нарративный обзор научной литературы, опубликованной за период с января 2013 г. по март 2023 г. в электронных базах данных PubMed и Web of Science. Исследования считались приемлемыми, если они включали данные о нейробиологических механизмах регуляции аппетита, а также результаты клинических исследований препаратов центрального действия при расстройствах пищевого поведения. Релевантные исследования включались в обзор независимо от их дизайна. Для обобщения полученной информации использовался описательный анализ.

РЕЗУЛЬТАТЫ: В обзор включено 51 исследование. Анализ имеющихся нейробиологических и клинических данных позволил обосновать следующие фармакологические стратегии модуляции аппетита при расстройствах пищевого поведения: серотонинергическая, катехоламинергическая, аминокислотергическая и пептидергическая. Однако недостаточное количество клинических исследований с высоким уровнем доказательности затрудняет внедрение полученных данных в клиническую практику, что особенно актуально для подросткового возраста ввиду практически полного отсутствия рандомизированных контролируемых исследований в этой возрастной популяции.

ЗАКЛЮЧЕНИЕ: Прогресс в нейробиологическом понимании механизмов центральной регуляции аппетита открывает перспективу разработки новых фармакотерапевтических подходов, направленных на изменение паттернов пищевого поведения. Лечение расстройств пищевого поведения, безусловно, представляет собой гораздо более широкую проблему, не сводимую исключительно к коррекции объема потребляемой пищи. Тем не менее на определенных этапах лечения фармакогенная модуляция аппетита может играть важную роль в ряду комплексных биологических и психосоциальных интервенций. Трансляция нейробиологических данных в клиническую практику требует проведения большого числа клинических исследований для подтверждения долгосрочной эффективности и безопасности фармакотерапевтических подходов и разработки персонализированных алгоритмов лечения различных вариантов расстройств пищевого поведения в разных возрастных популяциях.

Keywords: *eating disorders; anorexia nervosa; bulimia nervosa; binge-eating disorder; appetite regulation; pharmacotherapy; adolescence*

Ключевые слова: *расстройства пищевого поведения; нервная анорексия; нервная булимия; компульсивное переедание; регуляция аппетита; фармакотерапия; подростковый возраст*

INTRODUCTION

Eating disorders (EDs) are increasingly becoming the focus of the attention of researchers due to their growing prevalence in different age groups and significant contribution to the global disease burden [1]. There are three main types of EDs: anorexia nervosa, bulimia nervosa, and binge eating disorder; there are also various atypical and unspecified forms [2].

Anorexia nervosa is characterized by severe weight loss, accompanied by an intense fear of gaining weight, a strict

and restrictive diet, and purging behavior (self-induced vomiting, laxative abuse, use of diuretics, etc.) [3]. This type of ED is associated with the highest mortality rate among mental disorders [2]. Bulimia nervosa is characterized by recurring episodes of binge eating; each episode is followed by actions that aim to reverse the excess food intake and suppress the eventual weight gain (vomiting, taking laxatives, dieting for a long time, excessive exercise) [3]. Binge eating disorder is characterized by repeated episodes of eating large amounts of food, combined with a feeling of loss of control over this urge [3]. These episodes are often followed by feelings of shame, disgust, or depressive thoughts, but, unlike bulimia nervosa, no action is usually taken to prevent weight gain [3].

Psychosocial interventions have traditionally been the primary method used to treat EDs, while pharmacotherapy has usually played a secondary role [4, 5]. Meanwhile, many exogenous substances are known to significantly alter appetite and affect the amount of food consumed, either decreasing or increasing it [6, 7]. These substances include both medicinal products and psychoactive substances (legal and prohibited) [8–12]. For example, some substances with addictive potential, in particular nicotine and psychostimulants, reduce appetite [8, 9]. This effect has been the reason for the use of amphetamine derivatives as anorectics in the treatment of obesity for several decades [10]. Many antipsychotics, on the contrary, increase appetite and cause weight gain [11]. An increase in appetite is also caused by certain psychoactive substances, such as cannabis [12].

Despite the fact that there are plenty of pharmacological substances that have the potential to affect appetite and eating behavior, there remains a clear shortage of drugs officially approved for the treatment of EDs. In the Russian Federation only one drug, the antidepressant fluoxetine, is approved for use in EDs, namely in bulimia nervosa[1]. In the United States, another drug is authorized for EDs treatment: lisdexamfetamine [13]. This psychostimulant, which is used in the treatment of attention deficit hyperactivity disorder, has recently been approved by the United States Food and Drug Administration, FDA, for use in binge eating disorder [13]. In addition to these two compounds, there are a number of drugs on the pharmaceutical market that are approved for the treatment of excess weight and obesity [14]. Presumably, these drugs may have therapeutic potential in EDs.

There is currently no consensus on pharmacotherapeutic algorithms for various types of EDs. Existing national guidelines and recommendations are not always consistent across the board [4, 5, 15]. In practice, psychotropic drugs in EDs are often prescribed to treat concomitant psychiatric symptoms (anxiety, depression, obsessions), as well as to address body image distortions and delusional thinking [15, 16]. The possibility of using drugs to directly influence the endogenous mechanisms of appetite regulation are often ignored. In our opinion, historical skepticism towards pharmacotherapeutic interventions is probably partly due to a lack of understanding of the neurobiological basis of EDs. Lately, the body of data from experimental and neurophysiological studies has significantly expanded our understanding of the neurobiological mechanisms that underlie eating behavior regulation.

The aim of this paper is to narratively review the available neurobiological data on the mechanisms of central regulation of eating behavior as a rationale to summarize pharmacological strategies for appetite modulation in EDs.

METHODS

The authors conducted a narrative review of scientific literature on the subject published from January 2013 to March 2023 in the electronic databases PubMed and Web of Science. This time interval was chosen because of the surge in scientific research in the field of neurobiology and treatment of EDs that has taken place over the past decade, including innovative pharmacotherapeutic approaches based on promising pharmacological strategies. The search terms included the keywords “eating disorders”, “anorexia nervosa”, “bulimia nervosa”, “binge eating disorder”, “appetite”, “eating behavior”, “obesity”, “neurobiology”, “pharmacotherapy”, “pharmacological strategies” and “drug treatment”, “antidepressants”, “antipsychotics”, and “psychostimulants”. The keywords used for the search combined two interconnected terms; for example: “eating disorders” AND “pharmacotherapy”.

Studies were considered eligible if they included data on the neurobiological mechanisms of appetite regulation and eating behavior, as well as the results of clinical

1 State Register of Medicines. Instruction for the medical use of fluoxetine [Electronic resource]. URL: http://grls.rosminzdrav.ru/Grls_View_v2.aspx?routingGuid=d3561b67-fc74-4378-a169-f1913e60459b.

studies of drugs for various types of EDs. Relevant studies were included regardless of their design. Since a number of relevant studies had been published before 2013, their results were also included in the review if they were deemed important. References from more recent publications included in the review were used to search for such studies. Descriptive analysis was used to summarize the obtained data.

RESULTS

A total of 51 studies were included. Of those, 40 papers were published from January 2013 to March 2023, and the remaining 11 were published earlier.

In this section we will delve into the neurobiological mechanisms of central regulation of eating behavior relevant to the known pharmacodynamic effects of drugs. Next, we will outline pharmacological strategies based on the targeted effect of drugs on the neurochemical mechanisms involved in appetite regulation. Each strategy will be supported by the results of clinical studies of the respective drugs in EDs. In conclusion, data will be presented on alternative, promising neurochemical targets for innovative approaches to EDs pharmacotherapy.

The neurobiological mechanisms of eating behavior regulation

Eating behavior regulation is a complex and multifactorial process. The endocrine system (hypothalamic-pituitary-thyroid axis, hypothalamic-pituitary-adrenal axis, sex hormones), conditioned reflex mechanisms (the type and smell of food), gastric interoception (a full stomach), changes in biochemical homeostasis (decrease in blood glucose), etc. all play an important role [17]. A detailed discussion of appetite and eating behavior regulation is beyond the scope of this review. Only those of the neurobiological mechanisms that are relevant to the pharmacodynamics of centrally acting drugs will be presented below.

Eating, in addition to replenishing energy, is associated with reward and reinforcement. The main neuroanatomical structures responsible for appetite and motivation to eat are the hypothalamus and the endogenous reward system. An increase or decrease in food intake is regulated by peptidergic neurons located in the arcuate nucleus of the hypothalamus [18]. There are two types of these neurons that have opposite effects on appetite.

Neurons of the first type (POMC neurons) produce polypeptide pro-opiomelanocortin (POMC) and are anorexigenic (appetite-suppressive). Post-translational changes in POMC create two active peptides: β-endorphin and α-Melanocyte-stimulating hormone (α-MSH). The former is a ligand for opioid receptors, and the latter is a ligand for type 4 melanocortin receptors (MC4Rs) [19]. MC4Rs are actively expressed in the neurons of the paraventricular nucleus of the hypothalamus, which are part of the central anorexigenic pathway [20].

Neurons of the second type (NPY/AgRP neurons) synthesize neuropeptide Y (NPY) and agouti-related peptide (AgRP), which have orexigenic (appetite-stimulating) effects [18]. Also, these neurons produce gamma-aminobutyric acid (GABA) [18]. GABA-mediated mechanisms can also play an important role in the orexigenic activity of NPY/AgRP neurons: many "anorexigenic" structures, including nearby POMC neurons, receive inhibitory GABAergic signaling from NPY/AgRP neurons [19].

Both types of peptidergic neurons of the hypothalamus receive afferent signals from different areas of the CNS, as well as from the periphery (from the stomach, intestines, pancreas, and adipose tissue) [21, 22]. The activity of these neurons is regulated by many neurotransmitters (monoamines, endogenous opioids, glutamate, and GABA), neuropeptides, and hormones (cholecystokinin, leptin, ghrelin, and others). For example, leptin synthesized by adipocytes stimulates POMC neurons and inhibits NPY/AgRP neurons, thereby reducing food intake [19]. Most endogenous modulators of eating behavior affect not only appetite and food intake, but many other physiological processes as well [21, 23]. Specifically, centrally synthesized orexins, besides to modulating eating behavior, play an important role in the regulation of the sleep/wake cycle. Orexinergic neurons are located in the hypothalamic nuclei and innervate various parts of the brain, mainly those areas where monoaminergic neurons are located [24].

Monoaminergic signaling is of crucial importance in the regulation of the orexigenic and anorexigenic activity of hypothalamic neurons [23]. An increase in serotonergic tone (an increase in the concentration of serotonin released from the axonal terminals of serotonergic neurons of the raphe nuclei) shifts the balance towards appetite suppression [25]. This effect is probably mediated by the stimulation of postsynaptic 5HT2C receptors on POMC neurons, which increases the anorexigenic activity of the latter [18, 23]. This subtype of serotonin receptors is actively expressed in the hypothalamus [26]. Knockout

of this receptor causes obesity in laboratory animals [27]. 5HT2C receptors blockade (especially in combination with H1-histamine receptors blockade, which is shared by a number of antipsychotics and some antidepressants) has been noted to induce weight gain [28]. Along with serotonin, the catecholaminergic mechanisms of appetite and food intake regulation are also important [29]. These mechanisms are complex and multidirectional, but to put it simply, an increase in catecholaminergic signaling leads to an increase in the anorexigenic pathway activity, which is confirmed by the known clinical effects of psychostimulants [13, 30].

Orexigenic and anorexigenic hypothalamic neurons are connected with the ventral tegmental area, and POMC neurons inhibit dopamine neurons located there [31]. The latter one innervate the ventral striatum (nucleus accumbens) and the amygdala. These dopaminergic projections are part of the mesolimbic pathway that plays a central role in the endogenous reward system [32]. It is assumed that the level of dopamine released in the nucleus accumbens is associated with the feeling of pleasure from various types of "pleasant" activities, including tasty food. Ingestion of palatable food activates the reward system, triggering the release of dopamine in the nucleus accumbens and amygdala, thus reinforcing the behavior that leads to overeating and "food addiction" [33].

Eating tasty food also affects the opioid system, inducing the release of endogenous opioid peptides [34]. Administration of an opioid receptor antagonist (GSK1521498) for 28 days to subjects with obesity comorbid with binge eating disorder has been shown to reduce palatable food intake [35]. It has been also demonstrated that opioid receptor antagonists increase the anorexigenic activity of the arcuate nucleus [19].

The functional activity of the reward system is controlled by the glutamatergic neurons of the prefrontal cortex, probably through an activating effect on GABAergic interneurons [36]. It is assumed that dopaminergic and glutamatergic dysfunctions might lead to dysregulation of the reward/reinforcement processes associated with food intake and/or to a lack of inhibitory control, constituting an important neurobiological mechanism for developing EDs [37].

Overall, the central regulation of appetite and eating behavior is mediated by a number of neurobiological mechanisms. The hypothalamus plays a key role. The activity of orexigenic and anorexigenic hypothalamic neurons is modulated by a variety of neurotransmitters, peptides, co-transmitters, and hormones. Dysregulation of the functioning of the endogenous reward system may also play an important role in the development of eating behavior patterns in EDs.

Pharmacological strategies for appetite modulation

The described neurobiological mechanisms of appetite regulation give us a rationale for a number of pharmacological strategies based on altering the functional activity of neurotransmission to target the central orexigenic and anorexigenic processes. In principle, four main strategies can be outlined: serotonergic, catecholaminergic, amino acidergic (glutamatergic), and peptidergic (opioid).

Serotonergic strategy

As noted above, increased serotonin concentration in synapses formed by the axons of serotonergic neurons extending from the raphe nuclei and hypothalamic peptidergic neurons leads to appetite suppression, probably due to a stimulation of 5HT2C receptors on POMC neurons of the arcuate nucleus of the hypothalamus, which leads to an increase in the activity of central anorexigenic structures [18, 23]. 5HT2C receptors can be pharmacologically stimulated in two ways: through indirect and direct agonism.

Fenfluramine, a drug that blocks serotonin reuptake, is an indirect agonist of serotonergic neurotransmission [38]. Fenfluramine was previously widely used for the treatment of obesity, then it was withdrawn from the market due to cardiac and pulmonary toxicity, and was recently approved for use in a number of countries for another indication: as an anticonvulsant in children with Dravet syndrome (but not in the Russian Federation) [38]. Almost all antidepressants are also indirect agonists of serotonin receptors [39–43]. Their antibulimic activity is well known and has been repeatedly confirmed with data from randomized controlled trials (RCTs) [39–43]. In the earliest studies on the topic, tricyclic antidepressants and monoamine oxidase inhibitors were found to be effective in reducing binge eating and subsequent purging behavior [39]. However, the severity of the side effects of these drugs limits their use in EDs [39]. Selective serotonin reuptake inhibitors (SSRIs) are preferred because of their more favorable safety profile. An 8-week, double-blind RCT in patients with bulimia nervosa (*n*=387) demonstrated that fluoxetine at a dose of 60 mg/day was superior to placebo in reducing the frequency of

binge eating and vomiting, as well as reducing symptoms of depression, carbohydrate cravings, and abnormal eating habits; at a dose of 20 mg/day, it had no significant effect [40]. In respondents fluoxetine demonstrated efficacy in preventing relapse in a 52-week follow-up study [41]. Fluvoxamine was also studied and demonstrated efficacy in preventing a bulimia nervosa relapse compared to placebo in a 15-week double-blind RCT (*n*=72) [42]. There is evidence of the efficacy of duloxetine in the treatment of binge eating disorder in patients with depressive disorder: a 12-week double-blind RCT (*n*=40) demonstrated its superiority over placebo in reducing the frequency of binge episodes, the body weight, and the severity of psychopathological symptoms [43]. It should be noted that not all antidepressants have been evaluated in RCTs in patients with EDs. In general, despite the reduction in the frequency of binge episodes, antidepressants (with rare exceptions) do not lead to a significant change in the body weight [39–43]. We should also note that not all of the studied antidepressants have a selective effect on serotonergic neurotransmission. Non-selective drugs also enhance the activity of catecholaminergic neurotransmission; so, considering them within serotonergic strategy is not entirely correct.

The second way to stimulate 5HT2C receptors in the hypothalamus is direct agonism. A selective 5HT2C serotonin receptor agonist, lorcaserin, is available in many countries (but not in the Russian Federation) [44]. It reduces appetite and suppresses hunger, helping to reduce the food intake. Lorcaserin is approved for the treatment of obesity, and it may have therapeutic potential for EDs associated with overeating [44].

Conversely, the 5HT2C receptor antagonism should have the opposite effects: increased appetite and increased food intake. This is confirmed by the known side effects of antipsychotic drugs, e.g. clozapine and olanzapine — both are potent blockers of 5HT2C receptor and cause the most pronounced weight gain among antipsychotics [45]. Atypical antipsychotics have been repeatedly considered as potential treatments for anorexia nervosa. A meta-analysis of seven RCTs demonstrated a moderate effect on weight recovery in patients with anorexia nervosa for olanzapine and no effect for risperidone and quetiapine [46]. Another meta-analysis confirmed the efficacy of olanzapine in the treatment of anorexia nervosa, namely in increasing body mass index [47]. It should be noted that although we consider the effect of antipsychotics on appetite and eating behavior to be part of the serotonergic strategy, other neurochemical mechanisms are likely to be also involved (for example, blockade of histamine receptors). For some drugs, the neuroendocrine effects associated with hyperprolactinemia (due to dopamine receptors blockade in pituitary lactotrophs) may come to the fore. Other effects of antipsychotics, including peripheral ones (effects on the liver, pancreatic β-cells, adipose tissue, and skeletal muscles), can also play a significant role in changing eating behavior and increasing body weight [45].

In addition, the role of the 5HT2C serotonin receptor in the regulation of appetite, eating behavior, and body weight is not that clear. The only drug approved for the treatment of bulimia nervosa, fluoxetine, is known to block (similarly to clozapine and olanzapine) 5HT2C receptors [48].

Catecholaminergic strategy

The efficacy of psychostimulants in reducing body weight has long been known. The main pharmacodynamic effect of these drugs is an increase of the synaptic concentration of catecholamines (dopamine and norepinephrine) [49]. As noted above, an increase in catecholaminergic afferentation (as well as serotonergic one) shifts the balance between the orexigenic and anorexigenic activity of hypothalamic neurons towards appetite suppression. It is likely that some other mechanisms, including peripheral ones, are also involved in weight loss induced by psychostimulants [29, 50].

Given the efficacy of psychostimulants in the treatment of obesity, they have been studied as therapeutic agents for EDs. Lisdexamfetamine is currently on the market in a number of countries (not in the Russian Federation) for the treatment of binge eating disorder [13]. The results of an 11-week double-blind RCT in patients with binge eating disorder (*n*=255) demonstrated that lisdexamfetamine was superior to placebo in reducing binge days [51]. Analysis of secondary efficacy parameters confirmed its superiority over placebo in reducing compulsive overeating and the severity of obsessive-compulsive symptoms [52]. Another double-blind RCT confirmed the safety and efficacy of lisdexamfetamine in patients with binge eating disorder (*n*=418) and provided evidence that its continued use for six months was superior to placebo in preventing relapse [53].

The amphetamine derivative sibutramine is used to treat obesity and could theoretically be useful in the treatment of EDs. A multicenter 24-week RCT of sibutramine efficacy in binge eating disorder (*n*=304) confirmed its efficacy in reducing binge episodes, weight, and associated symptoms

such as cognitive restraint, disinhibition, and hunger [54]. It should be noted that sibutramine increases the functional activity of both catecholaminergic and serotonergic neurotransmission [55], thereby exploiting (similarly to nonselective antidepressants) both monoaminergic strategies. Another sympathomimetic, phentermine, has been approved (in combination with topiramate, which is discussed below, as part of an amino acidergic strategy) for the treatment of obesity in a number of countries (not in the Russian Federation) [30].

Bupropion (not approved in the Russian Federation) is an antidepressant with similar pharmacodynamic effects to those of psychostimulants. It blocks norepinephrine and dopamine reuptake but, unlike psychostimulants, does not have an addictive potential [56]. Atomoxetine, a norepinephrine reuptake inhibitor, used to treat attention-deficit hyperactivity disorder in children, adolescents, and adults, has also a similar mechanism of action [57]. Bupropion as monotherapy is contraindicated in subjects with ED due to a high risk of seizures [58]. Bupropion in combination with naltrexone is approved in several countries for the treatment of obesity [59] and hypothetically might be useful in EDs. Atomoxetine, according to a small, single-center, 10-week RCT (n=40), can reduce binge eating frequency and body weight in binge eating disorder compared with placebo [60].

The opposite effect on the catecholaminergic neurotransmission (specifically, dopamine receptors blockade), as noted above, may contribute to the weight gain observed during the use of antipsychotics. This is confirmed by the fact that partial agonists of dopamine receptors (aripiprazole, cariprazine, and brexpiprazole) cause less weight gain of compared to antagonists [28].

In addition, it should be emphasized once again that eating behavior patterns are determined not only by the hypothalamic mechanisms of appetite regulation; the endogenous reward system also plays an important role. The functional activity of this system can be modulated by centrally acting drugs, in particular those drugs that affect the functional activity of the catecholaminergic neurotransmission [61, 62]. Specifically, antipsychotics suppress the reward system by blocking dopamine receptors in the mesolimbic dopaminergic pathway [62]. Therefore, the direction and severity of the pharmacological effect of catecholaminergic drugs on eating behavior will be largely determined by the sum of complex and multidirectional effects on the orexigenic/anorexigenic structures of the hypothalamus and on the reward system [62].

Amino acidergic (glutamatergic) strategy

Among the drugs with therapeutic potential in EDs, topiramate and zonisamide can be considered within the framework of the amino acidergic strategy. The exact mechanism how these drugs influence eating behavior and body weight has not been established. It is assumed that by altering the activity of voltage-gated ion channels, these drugs change the balance between the excitatory glutamatergic and inhibitory GABAergic signaling received by hypothalamic peptidergic neurons that regulate appetite [30]. Open-label clinical studies confirm that zonisamide can reduce binge eating and body weight in the short term (12 weeks) and at the 1-year follow-up, but is poorly tolerated, resulting in frequent patient withdrawal [63, 64]. Clinical studies of topiramate confirm its positive effect in reducing the frequency of binge episodes and body weight. A meta-analysis of three RCTs confirms the efficacy of topiramate in the treatment of binge eating disorder [65]. The combination of topiramate with the psychostimulant phentermine is used to treat excess weight, including in pediatric patients [66]. With this combination, the dose of phentermine may be reduced, which minimizes the risk of addiction and cardiovascular side effects [67].

Therapeutic use of ketamine, a dissociative anesthetic the effects of which are mainly mediated by its NMDA receptor antagonism, can be also considered within the amino acidergic (glutamatergic) strategy [68]. Due to its rapid clinical effect in depression [69], ketamine is extensively studied for other psychiatric indications, including EDs [70]. Preliminary clinical data on the efficacy and safety of ketamine in EDs suggest its therapeutic potential, but this should be confirmed in RCTs [70]. An interesting hypothesis regarding the possible augmentation of ketamine effect in anorexia nervosa by the addition of dietary supplements containing zinc also requires clinical confirmation. Zinc is known to be an allosteric modulator of the NMDA receptor, and is deficient in individuals with anorexia nervosa [71].

Peptidergic (opioid) strategy

The competitive μ-opioid receptor antagonist naltrexone has been approved (in combination with bupropion) in a number of countries (not in the Russian Federation) for the treatment of obesity [59]. Naltrexone itself only

slightly reduces body weight but has synergism with the pharmacodynamic effects of bupropion [59]. Blockade of μ-opioid receptors, on the one hand, activates the anorexigenic neurons of the hypothalamus (probably due to the elimination of negative feedback mediated by β-endorphin) and, on the other hand, blocks the reinforcement/reward [19]. Given the efficacy of the naltrexone and bupropion combination in obesity, it might have a therapeutic potential in EDs. The effect of this combination in binge eating disorder was evaluated in a 12-week placebo-controlled RCT (*n*=22), which demonstrated no significant superiority over placebo [72]. According to the authors, this was due to the insufficient statistical power of the study, therefore larger-scale RCTs are required [72].

Novel neurochemical targets

Within the framework of the discussed pharmacological strategies, in addition to the neurochemical targets that are addressed by existing drugs, some other targets that are promising for the development of innovative approaches to the pharmacotherapy of EDs can be identified.

Specifically, these novel targets include endocannabinoid receptors. Endocannabinoids, by means of retrograde neurotransmission, regulate the release of dopamine in the neuroanatomical structures related to the reward system [73]. Blocking endocannabinoid receptors may help reduce binge eating disorder symptoms and body weight [74]. In a multicenter RCT (*n*=289), the endocannabinoid receptor antagonist rimonabant caused significantly greater weight loss in the treatment of patients with binge eating disorder compared to placebo [74].

Psychedelics (that bind to serotonin receptors and change the activity of serotonergic processes) are now increasingly being considered as potential therapeutic agents for EDs [75, 76]. A preliminary study on the effects of ayahuasca, a psychedelic brew used for rituals in South America, demonstrated a reduction in ED symptoms as assessed by the patients themselves (*n*=13) [75]. A substance with psychedelic activity, psilocybin, is being considered as potential treatment for depressive and anxiety disorders, and it is also being studied for possible beneficial effects in patients with anorexia nervosa [76].

Given the effect of orexin neurotransmission on a number of physiological functions, including food intake, orexin receptor antagonists are viewed as agents with therapeutic potential in various neuropsychiatric disorders, including EDs [77].

Another promising neurochemical target is related to trace amines, which are increasingly being considered in the context of psychiatric disorders [78]. In particular, the trace amine-associated receptor 1 (TAAR1) has recently been studied as a dopaminergic and glutamatergic neurotransmission modulator, making it a promising therapeutic target in EDs [79]. Interestingly, TAAR1 is also stimulated by amphetamine, the active metabolite of lisdexamfetamine [79]. The agonism of lisdexamfetamine at TAAR1 may mediate its ability to restore neurochemical dysfunction in the prefrontal cortex by compensating for impaired inhibitory control mechanisms.

DISCUSSION

Our review of the literature identifies four pharmacological strategies for modulating appetite and food intake in EDs: serotonergic, catecholaminergic, amino acidergic (glutamatergic), and peptidergic (opioid). Each strategy is substantiated in terms of the neurotransmitter mechanisms of central regulation of eating behavior. The clinical prospects of these strategies are supported by the results of clinical studies of various classes of centrally acting drugs in different types of EDs. The two drugs with the highest quality of evidence to date are fluoxetine for bulimia nervosa [40, 41] and lisdexamfetamine for binge eating disorder [51, 53]. No single drug has a sufficiently strong evidence for anorexia nervosa, although meta-analyses suggest a possible moderate efficacy for olanzapine [46, 47]. It should also be noted that the majority of clinical studies in EDs have been short-term (8 to 15 weeks) [40, 42, 43, 51, 60, 63, 72], with the longest study lasting 52 weeks [41]. Given the propensity of EDs to relapse [2, 3], the long-term efficacy and tolerability of drugs cannot be assessed based on the available data.

Strengths and limitations

The strength of this narrative review is in its summary of the current neurobiological and clinical data supporting the possibility of pharmacological modulation of appetite and eating behavior. To our knowledge, this is the first publication to describe precise pharmacological strategies for appetite modulation in EDs based on the neurobiological mechanisms of regulation of eating behavior, on the one hand, and the results of clinical studies, on the other. A limitation of this review is that a number of relevant studies on this topic may have been missed, since a systematic search strategy was not used for the purposes of the

review. In addition, the methodological quality of the data obtained was not sufficiently high in some cases; many of the included studies had methodological shortcomings. The high heterogeneity of the endpoints and results of the studies made it very difficult to generalize the data obtained and prevented us from formulating practical conclusions regarding the pharmacotherapy of EDs.

Implications for future research and practice

This review of the literature demonstrates that the efficacy of centrally acting drugs in EDs associated with overeating (bulimia nervosa and binge eating disorder) has much stronger evidence than in anorexia nervosa. However, such dichotomy of eating habits based on the opposite changes in appetite and the amount of food consumed is not entirely correct. Within the same ED, a patient may have a combination of various patterns of eating behavior, manifested by both an increase and a decrease in food intake, which significantly limits the therapeutic potential of the pharmacological correction of ED. In addition, treating EDs is a much broader issue not limited to changes in appetite and food intake. However, at certain stages of treatment, pharmacological modulation of appetite may play an important role in a number of multi-targeted biological and psychosocial interventions aimed at ED correction. The neurobiological and clinical data collected in recent years inspire cautious optimism in this regard. Unfortunately, today, given the complexity of EDs treatment and the lack of high-quality clinical studies, it seems premature to talk about implementing the available data into clinical practice (especially in anorexia nervosa). Developing evidence-based guidelines and recommendations requires a large number of further studies.

One of the most important areas for future research is to evaluate the efficacy and safety of drug treatment for various types of EDs in adolescence. Despite a high prevalence of EDs among adolescents [1,2], there are virtually no RCTs of drug treatment in the adolescent population [80]. Meanwhile, the age factor undoubtedly makes a significant contribution to the efficacy and safety of pharmacotherapy. Adolescence presents particular challenges, and not only because of the high prevalence of EDs and their transnosological nature. Adolescence is characterized by active processes of neurobiological maturation of the CNS associated with significant structural and functional changes [81]. On the one hand, these changes may be associated with an absence or distortion of the expected drug-induced effects. On the other hand, it cannot be ruled out that the use of centrally acting drugs in adolescence, a critical period in CNS development, can change the neurodevelopmental trajectories of the brain structures targeted by these drugs, and the structures connected with them [82]. Large-scale long-term studies are needed to comprehensively assess the possible negative (including long-term) consequences of EDs pharmacotherapy in adolescence.

CONCLUSION

EDs are a global health problem that affects different age groups and requires the development of effective treatment. Over the past decade, great effort has been poured into the pharmacological treatment of EDs. Yet the pharmacotherapy options for these disorders remain limited. At the same time, the progress made in our neurobiological understanding of the mechanisms of appetite and eating behavior regulation opens up vast prospects in developing new therapeutic approaches that could alter patterns of eating behavior. The translation of neurobiological data into clinical practice requires a large number of clinical studies to confirm the long-term efficacy and safety of various pharmacotherapeutic approaches and develop personalized treatment algorithms for various types of EDs, specifically in adolescents.

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