

The role of nutrients and probiotics in treatment of depression

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ABSTRACT

Currently, a growing amount of data is emerging on the role of various environmental factors (nutrients, gut microbiota, etc.) on formation of depression. The impact on these factors can be effective not only in treatment of major depressive disorder, but also in its early prevention. Therefore, a more detailed study of environmental factors in depression can lead both to a better understanding of the etiology and pathogenesis of the disorder and to optimization of approaches to its treatment. The aim of the review was to assess the potential role of a number of environmental factors associated with nutritional aspects and characteristics of individual microflora, as well as to review the prospects of a strategy for affecting these factors in treatment and prevention of depression.

Key words: depression, nutrients, vitamins, probiotics, microbiome, environmental factors.

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Роль нутриентов и пробиотических препаратов в терапии депрессии

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РЕЗЮМЕ

В настоящее время появляется все больше сведений о роли различных экологических факторов (особенностей питания, бактериальной флоры человека и проч.) в формировании депрессии. Воздействие на указанные факторы может быть эффективно не только в лечении депрессивного расстройства, но и его ранней профилактике. Таким образом, более подробное изучение роли экологических факторов в формировании депрессии может способствовать как лучшему пониманию этиопатогенеза данного заболевания, так и оптимизации подходов по борьбе с ним.

Цель обзора: оценить потенциальную роль в формировании депрессии ряда экологических факторов, связанных с нутритивными аспектами и особенностями микрофлоры индивида, а также перспективность стратегии воздействия на данные факторы в лечении и профилактике депрессивного расстройства.

Ключевые слова: депрессия, нутриенты, витамины, пробиотики, микробиом, экологические факторы.

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Источник финансирования. Авторы заявляют об отсутствии финансирования при проведении исследования.

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INTRODUCTION

Depression is a chronic mental disorder with complex etiopathogenesis. Numerous biological and environmental factors are increasing depression risks. According to the World Health Organization (WHO), over 264 million people worldwide suffer from depressive disorders, which is associated with high rates of disability [1].

However, despite the widespread prevalence, clinical diversity, and numerous negative consequences of depression, most studies on its treatment and prevention are now focused on neurotransmitter disorders. As a result, not a single drug has appeared in recent years with a fundamentally new mechanism of action and significant superiority in terms of therapeutic efficacy. Moreover, about one third of depressed patients do not respond to standard therapeutic approaches [2].

The search for and correction of new potential risk factors for depression are not given due attention, although there is more and more information about the role of various environmental factors (dietary habits, human gut microbiota, etc.) in the pathology of this disease [2]. Changes in various nutrients, biologically active substances, and individual microflora can affect synthesis of neurotransmitters, a number of metabolic pathways, and mood regulation [4, 5]. In this regard, the regulation of these factors can be effective not only in the treatment of depressive disorders, but also in their early prevention. Therefore, a more detailed

study on the role of environmental factors in depression risks can contribute to both a better understanding of the disease etiopathogenesis and optimization of strategies to oppose it.

The aim of the review was to assess the potential role of a number of environmental factors associated with nutritional aspects and characteristics of individual microflora, as well as to review the prospects of a strategy for affecting these factors in treatment and prevention of depression.

Rationale for nutrient augmentation of antidepressant therapy

Nutritional factors, microbiota and mental functions of an individual (including mood regulation) are in a complex, close relation with one other. Thus, biologically active substances and nutrients are processed by the gut microbiota and are able to affect regulation of hormonal, neurotransmitter, and signaling pathways of both the gastrointestinal tract (GIT) and the central nervous system (CNS) [4]. There are literature data that unhealthy diet in terms of a nutrient content significantly increased the risk of depression [2]. The most detailed information in the scientific literature on these issues is presented about vitamins (folates, vitamin D) and polyunsaturated fatty acids (PUFAs).

FOLATE USE IN THE TREATMENT OF DEPRESSION

Folate (vitamin B9) is a collective term for a class of compounds belonging to the group of water-sol-

uble vitamins [5]. This class of compounds plays an important role in one-carbon metabolism (OCM), including pathways for the biosynthesis of key amino- and nucleic acids. Folate deficiency is associated with a number of cardiovascular problems, neurological disorders, and diseases of the blood and reproductive system. Insufficient folate intake is often reported in populations where the intake of green vegetables and fresh fruits is reduced. Other foods rich in folates are legumes, grains, eggs, and liver.

Dietary folate intake is strongly associated with blood homocysteine levels [6]. In the case of hyperhomocysteinemia, folate supplementation corrects this condition, which has been confirmed by a number of studies [6]. In studies of patients with cardiovascular disease (CVD) and high homocysteine levels, folic acid treatment significantly reduced homocysteine levels, while the administration of B6 and B12 did not have a similar effect [7]. Furthermore, patients with CVD and low folate levels have an increased risk of depression [8].

Several forms of folate were used in depression treatment studies. 5-MTHF – 5-methyltetrahydrofolate (metafolin, methylfolate) is a biologically active form of folate. This compound is the closest to the natural food form of folates, which easily penetrates into the central nervous system (unlike synthetic folic acid), does not require preliminary transformation in the liver with dihydrofolate reductase, and is immediately incorporated into the folate metabolism cycle. Moreover, its further biochemical metabolism (in particular, the delivery of methyl groups to the homocysteine – methionine cycle) does not depend on the genetic polymorphism MTHFR677C> T [5]. In most of the studies on the effect of folate on mood, it was 5-MTHF that was studied.

On the other hand, synthetic folic acid is much more widely studied in obstetrics, and its chemical stability makes it possible to use this particular form of folate as food fortification in several countries (USA, Canada, Brazil, Australia). In this regard, a huge amount of observational information has been accumulated on this folate form [5–7]. It was noted that food fortification with folates decreases the prevalence of depressive symptoms in the population. In men, this is mediated by an increase in plasma folate levels, while in women, this effect is not observed [5].

The effectiveness of several different forms of folate at different doses and in different categories of patients has been studied in association with depression. At the same time, studies with the addition of fo-

late to antidepressant therapy are more numerous and rigorous in design, in contrast to studies of independent folate therapy. In a randomized, placebo-controlled study, the group of women who received the antidepressant fluoxetine (20 mg) along with folic acid (500 mcg / day) had 94% of responders, while the group receiving fluoxetine with placebo had only 61% of responders ($p < 0.005$). In men in this study, the difference in the effectiveness between the groups was less significant, also a less significant decrease in homocysteine levels was observed compared with women. This, according to the authors of the study, indicates the need for large doses of folate in men. At the same time, to select the optimal doses, further studies of folate administration in combination with other antidepressants are required [6].

In another study with the same design ($n = 27$), where the dose of folic acid was 10 mg / day, in the group of patients receiving folate with fluoxetine (20 mg) after 6 weeks of treatment, the average score on the Hamilton Depression Rating Scale (HDRS) was significantly lower than in the placebo group receiving only fluoxetine [7].

L-methylfolate has also shown beneficial effects as adjuvant therapy in addition to traditional antidepressants [6]. In a double-blind, placebo-controlled study, standard psychotropic therapy in patients with depression and schizophrenia was successfully supplemented with methylfolate (15 mg) for 6 months. At the same time, clinical and social recovery was significantly accelerated compared with placebo, and, over time, the differences with the placebo group increased ($n = 123$) [5].

G.I. Papakostas et al. (2014) showed in a clinical study that L-methylfolate (15 mg / day), in addition to therapy in patients ($n = 75$) initially resistant to antidepressants belonging to selective serotonin reuptake inhibitors (SSRIs) contributed to overcoming therapeutic resistance. In this regard, the authors conclude that L-methylfolate at a dose of 15 mg / day can be considered an effective, safe, AND relatively well-tolerated agent for overcoming a partial response or a lack of response when using SSRIs in patients with depressive disorders [9]. In the extended 12-month open phase of this study, there were also positive results ($n = 68$) on sustained remission in patients receiving 15 mg of L-methylfolate a day [9].

Another biologically active form of folate, folinic acid (leucovorin, unlike folic acid, does not require conversion by dihydrofolate reductase in the liver), when additionally prescribed to patients with depres-

sive disorder who are resistant to SSRIs, has shown itself as a poorly effective remedy (the level of folate in patients in this study was initially normal) [2].

Based on a systematic review and meta-analysis of 3 randomized, controlled studies, it was concluded that folate may play a potential role as an adjunct to basic therapy for depression and cannot be used as stand-alone treatment [5, 6]. At the same time, there are suggestions that the addition of folate to antidepressant therapy may be useful for patients with depression, regardless of their initial folate status, as well as regardless of the presence / absence of a response to antidepressant therapy [2]. M. Fava et al. concluded that folates are effective and safe in some patients with depressive disorders, but more information is needed on the dosage and patient populations most suitable for folate therapy [6].

A number of researchers draw attention to the need for further long-term research (from 6 months to a year), because the effect of folate administration is slow and builds up over several months. Low doses for a long time are more preferable than high doses for short or even long term [6]. Large doses of folate can be dangerous for the nervous system in terms of antagonism with vitamin B12 and its deficiency, as well as in terms of provoking seizures. Moreover, it was shown that folic acid at a dose of more than 5 mg / day can cause agitation, hyperactivity, and insomnia and provoke hypomanic states in the case of a predisposition [5–7]. At the same time, there is evidence that unmetabolized folic acid (when prescribed in exceeded doses) can inhibit further folate metabolism and lead to aggravation of OCM disorders [5–7].

THE USE OF VITAMIN D IN THE TREATMENT OF DEPRESSION

Vitamin D is another important vitamin in the risk of depression and its therapy. It is obtained from food in the form of vitamin D2 (vegetables, mushrooms) and vitamin D3 (meat, fish, eggs) [10]. Despite this, very few foods are rich in vitamin D. The highest vitamin D content is found in animal products in the form of vitamin D3 in oily fish, egg yolks, meat, liver, and kidneys. Another important environmental factor in the synthesis of vitamin D by the body is sufficient ultraviolet (UV) exposure of the skin.

While the role of vitamin D in calcium homeostasis and the maintenance of bone metabolism has been studied well enough, its effect on the structure of the central nervous system still raises many questions. Vitamin D receptors are widely presented in the

brain structures which are responsible for affective disorders, which suggests the role of vitamin D in the mechanisms of depression [11–13]. Another important aspect was identification of frequent decreases in vitamin D levels in cases of seasonal affective disorder with depressive episodes in winter [13]. However, in subsequent randomized controlled trials, no unambiguous information was obtained on either a natural decrease in vitamin D in depression, or its effectiveness in the treatment of depressive disorder.

In the Iranian study, the use of vitamin D (oral vitamin D3 at a dose of 50,000 IU every two weeks) for 8 weeks in 76 patients with postpartum depression and decreased levels of 25[OH]D (less than 75 nmol / l) led to improvement of depressive symptoms and normalization of vitamin levels in the blood [14]. Therapy effectiveness was evaluated in three subgroups: vitamin D in combination with calcium supplements; vitamin D in combination with a placebo instead of calcium supplements; the placebo group alone. The Edinburgh Depression Scale (EDS) was used to assess the severity of depression. A decrease in the severity of depression was noted for both subgroups where vitamin D was used regardless of calcium augmentation. At the same time, a large-scale study on the use of vitamin D3 (400 IU / day) and calcium carbonate (1,000 mg / day) among 36,282 postmenopausal women did not reveal significant reduction of the risk of depression during therapy [15].

A meta-analysis by U. Gowda et al. did not reveal any positive changes in depression symptoms when using vitamin D either as monotherapy or in combination with antidepressants and other drugs [16].

THE USE OF OMEGA-3 POLYUNSATURATED FATTY ACIDS IN THE TREATMENT OF DEPRESSION

For a long time, polyunsaturated fatty acids (PUFAs) have been studied primarily in the context of their use for prevention of cardiovascular diseases. However, there is a growing amount of data on their role in mood regulation [17]. There are 4 classes PUFAs: ω 3, ω 6, ω 7, and ω 9 (this division into classes is based on the chemical structure – the position of the first double bond in relation to the carbon of the terminal methyl group) [17]. The most important PUFAs for the body are ω 3 and ω 6 [17].

The main representative of the ω 6 class is arachidonic acid (AA) [17]. It enters the body with food (vegetable oils, the largest amount is found in flaxseed oil) and is partially synthesized by the body,

which ensures its constant presence in the human body [17]. Such ω 3 PUFAs as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) enter the body only with food, their main source is fatty marine fish species [11, 17].

Potential mechanisms are currently being explored that could determine the antidepressant activity of ω 3 PUFA. In the last decade, the results of many experimental studies indicated that ω 3 PUFAs have a significant effect on inflammation, expression of apoptosis-related genes, oxidative stress, neurotrophic functions, and neurotransmitter systems [18]. EPA plays the most significant role in the anti-inflammatory activity of ω 3 PUFA. Clinical studies show that the use of EPA in comparison with placebo and DHA is more effective in a group of patients with biochemical markers of inflammation (elevated C-reactive protein (CRP)) [18].

Various studies have used fatty acids both as monotherapy and as an adjunct to standard antidepressant therapy. Different doses (from 1 to 6 g / day) and different duration of treatment (from several weeks to months) were used. Various sources of fatty acids have been studied: both pure eicosapentaenoic and docosahexaenoic fatty acids in combination or their isolated use, also fish oil and fatty acids obtained from plant seeds. However, dietary information was not analyzed in most studies [11, 17].

The results of studies on the effectiveness of ω 3 PUFAs have yielded ambiguous conclusions. At the initial stage in the research of this problem, very encouraging results were obtained. A positive effect was registered both for ω 3 PUFA monotherapy and for methods of augmenting the antidepressant effect [19]. Furthermore, it was noted that the use of ω 3 PUFA significantly reduced the risk of depression recurrence [20]. However, these studies were conducted in small cohorts without regard to the dose ratio of EPA and DHA. Subsequently, it was shown that therapeutic efficacy was revealed when using drugs containing high doses of EPA and low doses of DHA (2–4: 1 ratio or more), while the opposite combination (high doses of DHA and low doses of EPA) was not therapeutically effective in depression [20]. This result was confirmed by the meta-analysis, which showed that ω 3 PUFA preparations containing at least 60% EPA were effective in the treatment of depression and may be used for treatment of comorbid somatic symptom disorders [21].

Studies have been conducted on the use of preparations containing only EPA. EPA monotherapy at a

dose of 1 g / day for 8 weeks in patients with depressive disorders did not significantly reduce depressive symptoms as measured by the HDRS [19]. At the same time, the use of large doses of the drug (1.2–4 g per day) was significantly more effective [19]. However, in this study, EPA was used in conjunction with an antidepressant. The use of DHA in isolation at a dose of 2 g / day for 6 weeks had no significant effect on depressive symptoms [19].

Currently, on the basis of meta-reviews, it can be assumed that PUFAs can be considered as an effective method for augmentation of antidepressants. Drugs containing both EPA and DHA should be used, because these compounds are likely to have a synergistic effect on depressive symptoms. The effect of PUFAs on the lipid spectrum is of special interest, which is widely used in patients with depression in cases of metabolic syndrome associated with antidepressant therapy, eating disorders, and high consumption of high-calorie foods containing a large amount of animal fats [11].

THE USE OF ANTI- AND PROBIOTICS IN THE TREATMENT OF DEPRESSION

The study of microbiota-modifying therapeutic approaches is associated with obtaining both experimental and clinical data on the role of the microbiota – gut – brain axis in depression [22, 23]. This axis is mediated by bidirectional communication between the brain and the microbiota, which modulates immune and endocrine functions [24, 25]. The composition of the microbiota is associated with age, environmental factors, and dietary habits [22, 25].

In microbiome studies, the microbiota-depleting effects of antibiotics are used to study the effect of reduced microbial diversity on behavior [25]. Recent studies have identified links between frequent antibiotic exposure, especially during development, and many serious diseases, such as autoimmune pathology and mental health problems [26]. However, the use of antibiotics in experimental studies presents a number of problems. Antibiotics usually affect the body and its microbiome (or the transplanted microbiota) in three ways: depletion of the resident microbiota, subsequent enrichment of the antibiotic-resistant microbiota, and impact on the corresponding host tissues [27]. The effect of antibiotics on the host tissues is especially important when studying the central nervous system and behavior, since some antibiotics themselves can be neuroprotective or neurotoxic [28]. This can be seen as a limitation in behavioral research

using antibiotics to alter the composition of the microbiome.

Minocycline is an antibiotic of the tetracycline class. The pleiotropic activity of this drug, including anti-inflammatory, antioxidant, anti-apoptotic, anti-glutamatergic and monoaminergic effects, is widely discussed in the scientific literature [29]. In this regard, interest in the use of minocycline has expanded significantly, and it is considered as a potential candidate for treatment of affective disorders, both bipolar and unipolar ones. Currently, clinical trials of minocycline as monotherapy are underway [29].

Probiotics have been extensively studied in non-psychiatric populations and associated with improved gastrointestinal health, reduced inflammation, and temporary improvements in cognitive performance [30]. Diseases of the nervous system are already being considered a completely new area of probiotics application [26].

Currently, lactobacilli and bifidobacteria in the center of the probiotic market. They are widely used for correction and prevention of various pathological conditions (bacterial vaginosis, irritable bowel syndrome (IBS), diarrhea, obesity, allergies, urolithiasis).

Probiotics that can affect the severity of mental disorders are currently considered as psychobiotics [31]. The first study to evaluate the therapeutic efficacy of prebiotics or probiotics for depression was conducted over a decade ago, but about half of all existing studies were published in just the past two years, reflecting the rapidly growing interest in this area [32]. Most of the hypotheses associated with the potential therapeutic effect of psychobiotics on affective disorders are based on experimental animal models, behavioral tests, and neurophysiological indicators after courses of probiotics and prebiotics [32], as well as changes in the level of stress hormones, monoamines, and GABA receptors in the brain [32, 33].

While research on the use of probiotics for mental disorders is promising, there are conflicting reports on their effectiveness as augmenting agents [33]. Numerous studies have examined the effects of probiotics on mood in both healthy individuals and patients diagnosed with depression. Recent meta-analysis of data mostly confirms the positive effects of certain probiotics on mood [33]. Based on the results obtained, it is suggested that probiotics affect mood only in depressed patients and do not have an antidepressant effect in healthy individuals. Moreover, the antidepressant effects of probiotics are likely to be limited to

young adults and do not appear in those over 65 years of age [32].

The study on the prospects of probiotic use in depressed patients has several limitations. This is primarily due to different doses and duration of drug administration, which makes it difficult to compare studies. A similar problem is research of various species and strains of bacteria. Probiotics, which are likely to have an antidepressant effect, mainly belong to the *Bifidobacterium* and *Lactobacillus* genera. These genera contain many different species and strains, and their properties cannot be generalized [34]. For example, *Lactobacillus rhamnosus* (strain JB-1) did not affect mood or anxiety levels in healthy men, while *Lactobacillus casei* (strain Shirota) demonstrated the ability to improve mood in healthy volunteers with low baseline mood scores [35].

Probiotic bacteria can affect the body through various mechanisms that can be specific for the strain (e.g., lactic acid bacteria) or widespread among a variety of strains, including normalization of disturbed microbiota, inhibition of potential pathogens, production of beneficial metabolites or enzymes, and immunomodulation [32, 34]. However, the results of clinical studies are not convincing. There is very limited evidence for the effectiveness of probiotic or prebiotic interventions in altering microbial composition in mental disorders [36]. Conversely, probiotics led to changes in the microbial composition, but without affecting mood symptoms [37].

DISCUSSION AND CONCLUSION

Recent treatment strategies for depression consider the use of antidepressants as the first-choice tactic [11]. Despite market expansion for these drugs with the emergence of a new generation of antidepressants, including drugs with multi-receptor activity, there is no much progress in their efficiency – only 50% of patients manage to achieve stable remissions [11]. The side effects of antidepressants significantly affect treatment and reduce adherence to therapy [11]. Today, augmentation (enhancing the activity of antidepressants with the use of drugs that do not belong to the group of thymoanaleptics) is the main direction that is widely studied and used for treatment-resistant depressive conditions [11]. For this purpose, psychotropic drugs (antipsychotics, lithium salts, anticonvulsants) and hormonal drugs are used. However, the use of this approach increases the number of side effects due to both side effects of additional drugs and drug combinations.

Despite different mechanisms of functioning of various biologically active compounds, nutrients, and their interaction with microflora in the body, in most cases the key question remains, whether it is advisable to use these compounds in all patients or only in those who initially have their deficiency. Potential limitations in the therapeutic use of these compounds indicate difficulties in determining a deficiency of a particular nutrient in various populations [2, 3]. As a rule, in the population of developed countries, changes in such parameters are not clinically visible, which makes it difficult to diagnose them and determine their relationship with depression. At the same time, with regard to probiotics, it is noted that individuals with different genetic predisposition and variable contacts with microorganisms can react differently to identical drugs [4].

The need for further randomized studies to determine the efficiency, which will consider the difference in effect by subgroups, sex, presence / absence of deficiency, and other factors, is indicated for folates [5, 6], vitamin D [10, 12, 14], and fatty acids [17, 19]. For all these compounds, the study of approaches to therapy is carried out on a wide population of patients with depressive disorders, therefore, the effectiveness may be questionable not due to insufficient effect, but due to the phenomenological and biological heterogeneity of the samples and the absence of clearly defined control criteria (laboratory parameters).

Another promising direction in the context of this strategy is the study of not only individual isolated nutrients, but also complexes of dietary patterns in general [38]. Such an approach can help to establish the role of the mutual impact of various nutritional components on depression, as well as their interaction in the context of a number of body characteristics (such as the composition of gut microbiota). Moreover, modification of the entire diet may be a more effective and physiological method of preventing depressive disorder than correcting individual nutrients.

Therefore, even now, the use of nutrients and probiotics can be seen as a paradigm shift in the treatment of treatment resistant depression. At the same time, it is important to select a specific drug for augmentation based on laboratory screening, which makes it possible to apply a personalized approach to therapy.

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