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POSSIBILITIES OF CORRECTION OF FUNCTIONAL DISORDERS OF THE GASTROINTESTINAL TRACT IN PATIENTS WITH ANXIETY DISORDERS

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ABSTRACT

Functional disorders of the gastrointestinal tract have recently occupied a niche of the most common diagnoses in gastroenterology, recognized by morphological and physiological abnormalities. Functional disorders of the gastrointestinal tract are a heterogeneous group of disorders, including not only symptoms characteristic of functional dyspepsia (14.6%) in combination with changes in intestinal motility but also irritable bowel syndrome (irritable bowel syndrome, 31.7%) and constipation. These are diseases classified by gastrointestinal manifestations, including one of the following symptoms: impaired motor skills, visceral hypersensitivity, changes in the function of the mucous membrane and the immune system, changes in the intestinal microbiota, and changes in the processing of the central nervous system. According to several studies, mental disorders such as depression and anxiety are often accompanied by functional disorders of the gastrointestinal tract. Thus, it can be concluded that functional disorders of the gastrointestinal tract require a multidisciplinary approach for timely diagnosis and treatment. A recent global Internet survey of the Rome Foundation, in which 127 54 people from 26 countries participated, reported that 32 112 (43%) of the respondents met the criteria for at least one of the manifestations of functional disorders of the gastrointestinal tract. Given the high prevalence of the disease, it is necessary to clearly understand the possibilities of correcting functional disorders of the gastrointestinal tract. This will allow researchers and practitioners to approach the treatment and prevention of this pathology more meaningfully.

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Introduction

Functional disorders of the gastrointestinal tract are widespread among the general population. They are the cause of a significant number of requests for medical care, both at the primary and secondary levels. In recent years, a number of mechanisms for the occurrence of functional disorders of the gastrointestinal tract have been studied. These include disorders of the gut-brain axis **(Figure 1)**, the influence of diet, genetic factors, infections and disorders of the intestinal microbiota, mild inflammation of the mucous membrane, local immune activation, changes in intestinal permeability, impaired bile acid metabolism or abnormalities in the metabolism of 5-hydroxytryptamine (5-HT). There is no doubt that environmental

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conditions also play a significant role in the occurrence of this problem. Some scientists also claim that the level of development of a person's country of residence affects the prevalence of symptoms [1-3].

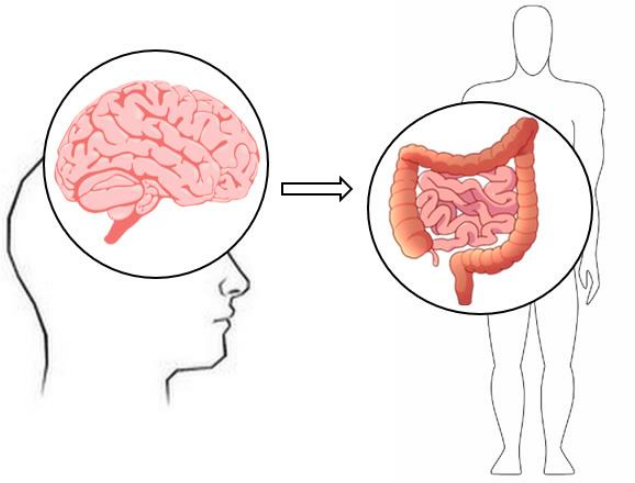

Figure 1. Neurohumoral brain-bowel axis

Comorbid anxiety and depressive disorders are widespread in patients with functional disorders of the gastrointestinal tract (FDGT) and among groups of patients with symptoms of FDGT. This is explained not only by seeking medical help. It has been suggested that the increased prevalence of concomitant psychiatric diseases in patients with FDGT reflects the fact that FDGT may be a primary manifestation of brain dysfunction or even primary somatization when the brain controls intestinal manifestations. However, the connection is more complicated. The authors of some studies claim that most often, gastrointestinal disorders begin to manifest earlier than the deterioration of the emotional state. Other studies also confirm this fact. They emphasize the importance of intestinal problems, cytokine reactions, and the patient's brain response to the symptoms, as mentioned above. If these conclusions are correct, then the elimination of gastrointestinal tract dysfunction is achievable because the intestine is more accessible than the brain, which can potentially cure not only FDGT but also concomitant mood disorders [4-6].

The Role of Emotions

People with different temperaments perceive business failures, unfulfilled dreams, betrayals of friends, or the death of loved ones in different ways. One way or another, anger is a normal emotional reaction to negative factors. Nevertheless, in psychological practice, anger often becomes the root cause of many mental, psychological and physical problems. Frequent uncontrolled anger can cause depression, sleep disorders, and psychosomatic and somatoform disorders. Anger can be divided into situational (that is, the experience of anger in a specific situation) and characteristic (a character trait that determines a predisposition to anger) [7, 8].

In one study aimed at assessing situational and characteristic anger Inventory-2 (STAXI), people with irritable bowel syndrome showed a higher level of anger; therefore, there may be a link between anger and symptoms of irritable bowel syndrome. Studies have been conducted on the effect of anger expression on somatic symptoms. It was found that people with functional dyspepsia showed more pronounced signs of depression, anxiety, and anger. One study comparing patients with irritable bowel syndrome and patients with Crohn's disease using the STAXI questionnaire showed that depression and characteristic anger were more significant in patients with irritable bowel syndrome. Previous studies of the relationship between anger with FDGT show that in the treatment of FDGT, it is advisable to take into account anger as a trait of the patient's character. According to a recent study, female patients with FDGT have higher rates of anxiety, which confirms the results of previous studies. Existing and transferred mental problems were also much more pronounced in the group with functional disorders of the gastrointestinal tract. These results confirm the results of previous studies, which separately distinguish concomitant diagnoses of anxiety, depression, and somatization in individuals with functional disorders of the gastrointestinal tract. FDGT is a chronic disease that can lead to the loss of a habitual lifestyle (for example, significantly reducing activity, and complicate work), leading to higher rates of anxiety and depression. The reverse situation is also obvious neglected depression and a high level of stress can cause the appearance and development of FDGT symptoms. However, there is still no exact answer whether higher rates of anxiety and depression in patients with FDGT compared to healthy people are the cause or consequence of FDGT [9-12].

The Role of Diet

Although the main role in the development of FDGT is assigned to psychoemotional factors and the interaction between the gastrointestinal tract and the central nervous system, the role of nutrition in this matter cannot be underestimated [13]. Many patients report an association between the use of certain foods and the symptoms of FDGT. However, the symptoms did not appear in double-blind studies. Nevertheless, eating behavior can alter the gastrointestinal tract microbiome, which may be a

leading factor for the manifestation of FDGT symptoms. It was found that fermentable oligo-, mono- and disaccharides and polyols (so-called FODMAP) are present in stone fruits, legumes, and products containing lactose, as well as in artificial sweeteners, aggravate symptoms due to their fermentation and osmotic effects. Studies using magnetic resonance imaging confirm that when FODMAPs are administered to healthy subjects, the small intestine swells due to an increase in the water content in the small intestine [14]. Although this did not cause symptoms in the experimental group, in patients with FDGT and altered sensory function, FODMAPs caused symptoms in some patients. Gluten sensitivity without celiac disease is another exciting concept. Some patients with irritable bowel syndrome and functional dyspepsia who do not have signs of gluten disease experience a significant improvement in symptoms after excluding gluten from their diet [15, 16]. Basic principles of treatment of functional disorder of the gastrointestinal tract in anxiety disorders are showed in **Table 1**.

Table 1. Basic principles of treatment of functional disorder of the gastrointestinal tract in anxiety disorders

Diet therapy	Medical treatment	Augmentation therapy	Cognitive behavioral psychotherapy
Eating behavior can alter the microbiome of the gastrointestinal tract	Central neuromodulators - dysfunction in the gut-brain axis (the bilateral neurohumoral connection between the gastrointestinal tract and the central nervous system) is the biological basis of symptoms and disorders leading to FDGT in anxiety disorders	A combination of neuromodulator treatment with behavioral intervention (e.g., hypnosis, cognitive psychotherapy – see below), the addition of tricyclic antidepressant or selective serotonin reuptake inhibitors, especially in the presence of a somatic component of pain, or, in some cases, a combination of low doses of a tricyclic antidepressant with selective serotonin reuptake inhibitors	It is recommended in case of ineffectiveness of lifestyle changes, nutrition, and pharmacotherapy for nine months
	Symptomatic therapy		

Central neuromodulators (antidepressants, antipsychotics, and other drugs aimed at the central nervous system) are increasingly being used to treat FDGT, which is currently recognized as a disorder resulting from disconnection in the relationship between the intestine and the brain. Dysfunction in the gut-brain axis (the bilateral neurohumoral connection between the gastrointestinal tract and the central nervous system) is the biological basis of symptoms and disorders leading to FDGT [15]. The gut-brain axis comes from a single embryological basis. In the embryo, the neural tube differentiates into the brain and spinal cord and sends down the ganglia to populate the developing endoderm. This eventually becomes the enteral nervous system. The nervous systems of the brain and intestines are "sewn up"; they have the same neurotransmitters and receptors. The actions of these neurotransmitters depend on their location. Therefore, a high level of serotonin can relieve depression and lead to diarrhea [16].

Consequently, using antidepressants and neuroleptics will affect mental disorders and chronic gastrointestinal symptoms. In addition to the central effects, antidepressants can strongly affect the physiology of the peripheral gastrointestinal tract, enhancing serotonergic and noradrenergic neurotransmission (and peripheral neurogenesis), which may explain some of their beneficial effects in FDGT [17]. Thus, there are grounds for the use of central neuromodulators by patients with FGT due to their peripheral gastrointestinal effect.

Antidepressants

Tricyclic Antidepressants

A distinctive feature of tricyclic antidepressants is a variable combination of serotonin (5-HT) and norepinephrine reuptake inhibition properties. Because of this dual action, tricyclic antidepressant has a more potent analgesic effect than other classes of antidepressants that only affect one monoamine system (selective serotonin reuptake inhibitors) [16]. However, this is likely to increase the frequency of side effects of tricyclic antidepressants relative to other classes of antidepressants caused by increased neurotransmission of 5-HT and norepinephrine, as indicated above. Most tricyclic antidepressants have an additional affinity for receptors [18]. Some of the receptors (for example, antagonism to the 5-HT2A and 5-HT2C receptors) may enhance their main (antidepressant and/or analgesic) properties.

In contrast, others may be responsible for the manifestation of side effects. For example, antagonism to muscarinic receptors-1 can cause classic anticholinergic side effects, including dry mouth, constipation, drowsiness, and blurred vision. In turn, resistance to α1-adrenergic receptors can lead to dizziness, drowsiness, and orthostatic hypotension [19]. In the context of the treatment of FDGT, some side effects may be helpful, for example, slowing down transit through the gastrointestinal tract due to anticholinergic properties in patients with irritable bowel syndrome with diarrhea, as well as increased appetite and weight gain in patients with functional dyspepsia with early satiety and weight loss [20].

Serotonin and Norepinephrine Reuptake Inhibitors

Like tricyclic antidepressants, serotonin and norepinephrine reuptake inhibitors primarily block the reuptake of both 5-HT and norepinephrine, thereby enhancing the neurotransmission of 5-HT and norepinephrine. As in the case of tricyclic antidepressants, the degree of inhibition of serotonergic activity in this class differs somewhat from noradrenergic activity in individual drugs of this class. Venlafaxine has a significant inhibitory effect on the reuptake of norepinephrine only at doses

of at least 225 mg [21]. The use of duloxetine, even in smaller doses, will lead to a strong effect on the 5-HT transporter and norepinephrine. In turn, milnacipran has a strong inhibition of norepinephrine reuptake. These drugs are largely devoid of additional funds to the receptor.

Consequently, they have fewer side effects than tricyclic antidepressants while maintaining their potential analgesic properties. However, side effects associated with increased neurotransmission of 5-HT and norepinephrine can occur with the same frequency; in addition, the standard situation is nausea when using duloxetine or an increase in blood pressure when using venlafaxine. Thus, these drugs can be used to treat chronic somatic symptoms, including neuropathic pain and functional somatic syndromes such as fibromyalgia which often accompany functional disorders of the gastrointestinal tract [21].

Tricyclic antidepressant class drugs are central first-line neuromodulators for treating irritable bowel syndrome. In particular, amitriptyline and imipramine can reduce diarrhea and improve sleep quality. Desipramine and nortriptyline are recommended to be used if a less anticholinergic or antihistamine result is expected. Drugs from the class of selective serotonin and norepinephrine reuptake inhibitors have fewer side effects than tricyclic antidepressants. At the same time, they have a great potential to improve their overall well-being [22]. Selective serotonin reuptake inhibitors (selective serotonin reuptake inhibitors) can be used in irritable bowel syndrome if the patient has an increased sense of anxiety. At the same time, abdominal pain or diarrhea does not bother him enough to put the fight against them as a priority [23].

Antispasmodics

Guanylate Cyclase-C Receptor Agonists

One of the last types of visceral analgesics is associated with the directed stimulation of the guanylate cyclase-C receptor in the intestine. The cause of the analgesic effect is several intracellular reactions starting with the stimulation of guanylate cyclase-C, which leads to the production of intracellular cyclic guanosine monophosphate [24]. Cyclic adenosine monophosphate is transported into the extracellular space, simulating the conductive properties of nociceptive neurons in the submucosa. This theory is based on numerous animal studies and is effective in combating the pain symptoms of irritable bowel syndrome. The effect of cyclic guanosine monophosphate stimulation on fluid excretion leads to accelerated passage through the intestine, which limits its use in patients with a predominance of constipation. Linaclotide (not licensed in the Russian Federation) was the first substance available for clinical use after its effectiveness in irritable bowel syndrome was proven, followed by plekanatide (not licensed in the Russian Federation), with the same indications. It has been proven that their effect on pain syndrome in FDGT develops gradually, usually during the first two months of treatment [25].

Agonists/Antagonists of Peripheral Opioid Receptors

Stimulation of visceral m-receptors has long been considered a first-line treatment for conditions accompanied by chronic diarrhea, including irritable bowel syndrome-D. A person uses opioids of various modes of action (central or peripheral) for a long time. At the same time, the discovery and use of loperamide (a μ-receptor agonist that does not penetrate the blood-brain barrier) was a real breakthrough. However, the limiting factor was that a significant proportion of patients experienced increased abdominal pain and constipation [26]. A new therapeutic variant, eluxadoline (not licensed in the Russian Federation), has an agonistic effect against the μ- and κ-receptors and an antagonistic effect against the δ-receptors. Animal studies have shown that eluxadoline can reduce visceral hypersensitivity and normalize stool in patients with irritable bowel syndrome and diarrhea. At the same time, this drug can be effective in a broader range of doses compared to loperamide [27]. Significant advantages of this drug are the absence of signs of potential overdose or effects of opioid withdrawal after discontinuation of treatment; in addition, there are no major effects of stimulation of opioid receptors. Some authors have conducted large-scale studies of the impact of the drug on groups of patients with different doses (75 mg and 100 mg twice a day). Both study groups showed improvement in general well-being, abdominal pain reduction, and stool normalization within 12-26 weeks [28]. However, the question of the increased incidence of pancreatitis associated with treatment with eluxadoline, both in the baseline study and in post-marketing observation, requires a thorough study of the known risk factors for pancreatitis in general among patients with irritable bowel syndrome-D. So eluxadoline should not be taken in patients with liver diseases or who have undergone cholecystectomy [29].

Agonists/Antagonists of Serotonin Receptors

Studies of alosetron, a 5-HT3 receptor antagonist, have shown a reduction in abdominal pain in women with irritable bowel syndrome D. Moreover, the first studies of this drug showed severe side effects, in particular, constipation and ischemic colitis. But repeated studies with smaller dosages showed minimal complications [30]. A recent prospective open investigation in the USA, where alosetron (not licensed in the Russian Federation) was prescribed to women with irritable bowel syndrome-D, did not reveal serious side effects according to the 0.5 mg twice daily regimen [31]. In Asia, another 5-HT3 receptor antagonist, ramosetron (not licensed in the Russian Federation), is approved for treating irritable bowel syndrome-D in both men and women and has a similar effect on normal bowel function. Ondansetron, unlike alosetron and ramosetron, did not have a significant effect on abdominal pain. Prucalopride (Vegaprate in the Russian Federation), a selective 5-HT4 agonist, the main indication for use is the treatment of chronic constipation due to its effect on the gastrointestinal tract, which leads to an increase in the number of bowel movements and a decrease in the severity of symptoms associated with constipation [31].

Augmentation Therapy

The most practical concept is augmentation therapy, i.e., combining treatment methods in a specific clinical case when the therapeutic effect of each drug described above is not enough [32]. Instead of altogether abandoning one such (suboptimal) neuromodulator, it may be helpful to add other neuromodulators, sometimes in lower doses, to minimize the risk of side effects. Knowledge of receptor affinity, peripheral or central mode of action, together with the dominant symptoms in the patient, can lead clinicians to the correct selection of therapy and achieve additive effects [33]. There is no formal evidence in favor of augmentation therapy for FDGT, but it is assumed based on empirical data and experience in treating depression as the main disease [34]. Examples of augmentation: the combination of neuromodulator treatment with behavioral intervention (for example, hypnosis, cognitive psychotherapy), the addition of tricyclic antidepressant or selective serotonin reuptake inhibitors, especially in the presence of a somatic pain component, or, in some cases, a combination of low doses of a tricyclic antidepressant with selective serotonin reuptake inhibitors.

Cognitive Behavioral Psychotherapy

Psychotherapeutic correction methods play an important role in treating patients with FDGT. These include CBP – cognitive behavioral psychotherapy, interpersonal psychodynamic psychotherapy, gastrointestinal hypnotherapy, etc. These techniques have shown effectiveness in meta-analyses in the treatment of FDGT, in particular irritable bowel syndrome, in face-to-face and remote formats [35]; thus, the Russian Gastroenterological Association recommends the use of CBP when lifestyle changes, nutrition, and pharmacotherapy are ineffective for nine months. The "Standard CBP Protocol" is aimed at reducing the stress response to the events of the patient's daily life, and the "interoceptive protocol" focuses on reducing the anxiety response to visceral symptoms (reducing the fear of symptoms of FDGT). Protocols help the patient to "work" with both general and specific anxiety, to form awareness and trust in his body, and not to gastrointestinal anxiety; they help to create disease-oriented behavior. DeCola (2001) suggested using a hierarchy of distress stimuli correlating with the patient's gastrointestinal anxiety.-intestinal anxiety (food, situations) [36]. Thanks to this technique, according to the received hierarchy of stimuli, the patient controls his physiological hyperexcitation utilizing breathing techniques and muscle relaxation. Ljótsson *et al*. (2011) presented exposure therapy or mindfulness-based stress reduction therapy and acceptance and commitment therapy [37]. These behavioral techniques have shown great effectiveness in reducing general and gastrointestinal anxiety, reducing the symptoms of FDGT (in particular, irritable bowel syndrome), and improving patients' quality of life. Cognitive behavioral hypnotherapy proposed by Golden *et al*. (2007) included CBP and hypnotherapy (gut-directed hypnotherapy), which allows the patient, through self-hypnosis training, to manage specific gastrointestinal anxiety [38] situationally. Thus, it is possible to fully compensate for the dysregulation of the gastrointestinal tract in a patient only through the interdisciplinary interaction of a psychiatrist-psychologist-gastroenterologist.

The Relationship between Diet, Microbiota, and Endocrine Cells

The foods we use work as prebiotics for intestinal bacteria. Accordingly, the microflora of our intestines directly depends on the quality of the food we eat [39-41]. It is well-known that our intestinal bacteria ferment undigested food residues into methane, hydrogen, and short-chain fatty acids.

In addition to monosaccharides and disaccharides, consisting of one and two molecules, large-molecular carbohydrates are also contained in human food. Neem includes, for example, starch and glycogen (polymers from glucose), fructans (polymers from fructose), and galactans (polymers from galactose).

A considerable number of enzymes are synthesized in the human body that can break down starch and glycogen into glucose molecules. However, enzymes that break down bonds in fructans and galactans are practically absent in humans. In the small intestine, only 5-15% of the fructans and galactans received from food are absorbed, and the rest of the carbohydrates enter the colon, causing severe bloating, pain, and diarrhea.

It should be noted that fructans and galactans are very common in the daily diet. They are found in large quantities in legumes, cabbage, root vegetables, nuts, and flour.

That is, fructans and galactans are substrates for several bacteria. They cause adverse changes in the intestinal microflora, especially in patients with irritable bowel syndrome. People with irritable bowel syndrome generally have fewer bifidobacteria in their feces than healthy people. Moreover, the absolute and relative number of butyrate-producing bacteria decreases after a low-FODMAP diet [42]. Fecal microbiota transplantation changes the density of endocrine cells of the small and large intestines in patients with irritable bowel syndrome, which generally improves the quality of life and eliminates unpleasant symptoms [43].

The density of intestinal endocrine cells in patients with IBS is lower than in healthy people, probably due to the low density of stem cells and the low differentiation of these cells into endocrine cells.

Low consumption of FODMAP and fecal microbiota transplantation improve symptoms and quality of life, restoring intestinal endocrine cell density and improving quality of life. There is evidence that patients who do not respond well to the diet may be offered fecal intestinal microbiota transplantation [44-49].

Conclusion

FDGT, now more commonly referred to in modern literature (DGBI - disorders of gut-brain interaction, disorders of brain-intestine interaction), is often considered difficult to treat through various conservative therapy options, primarily due to the

limited effectiveness of pharmacological treatment. However, new research points to the importance of such treatments. We have included some treatment methods that are justified to achieve these effects and solve several problems simultaneously associated with the complex course of the disease observed with FDGT. The central role of the interaction of the intestine with the brain is increasingly emphasized as the most important for conceptual understanding, including in the persona attempts. In the presence of intermittent symptoms of mild severity (for example, worsening when eating, relief when defecating), peripheral neuromodulators are most often sufficient. But as the acute process becomes chronic, the intensity of symptoms increases, especially abdominal pain, nausea or vomiting, and extra-intestinal symptoms. The possibility of starting or adding central neuromodulators to existing treatment methods should be considered. It is also impossible to exclude the extremely high significance of patients' personal characteristics with FDGT. It is necessary to use biopsychosocial treatment tactics, including the possibility of correcting FDGT by combining pharmacotherapy and principles of cognitive behavioral therapy, which will allow the most effective management of these conditions.

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