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Exploring Approaches to Addressing Gastrointestinal Disorders in Patients with Anxiety

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Abstract

The present study aimed to investigate approaches to dealing with gastrointestinal disorders in patients with anxiety. Gastrointestinal functional disorders have recently become some of the most commonly diagnosed conditions in gastroenterology, characterized by structural and functional abnormalities. These disorders include a wide range of conditions such as functional dyspepsia (14.6%) with altered intestinal motility, irritable bowel syndrome (31.7%), and constipation. These conditions are characterized by various gastrointestinal symptoms, including impaired motility, visceral hypersensitivity, changes in the mucosal immune function, changes in gut microbiota, and disruptions in the brain's processing. Studies have shown that mental health issues, especially depression and anxiety, are commonly associated with gastrointestinal functional disorders. This suggests that a multidisciplinary approach is essential for the effective diagnosis and treatment of these disorders. A recent global survey conducted by the Rome Foundation, which included 127,054 participants from 26 countries, revealed that 43% of respondents met the criteria for at least one type of gastrointestinal functional disorder. With the high prevalence of these conditions, discovering effective strategies to address gastrointestinal dysfunction is crucial, enabling both researchers and healthcare providers to improve treatment and prevention strategies.

Keywords: Gastrointestinal functional disorders, Irritable bowel syndrome, Depression, Dyspepsia, Anxiety, Anxiety disorders

Introduction

Functional gastrointestinal disorders are prevalent among the general population and contribute significantly to the number of healthcare visits at both primary and secondary care levels. In recent years, various mechanisms behind these disorders have been explored. These include disruptions in the gut-brain communication, dietary influences, genetic factors, infections, imbalances in the intestinal microbiome, mild mucosal inflammation, immune activation in the gut, changes in intestinal permeability, as well as abnormalities in bile acid metabolism and serotonin (5-HT) processing. Environmental influences are also considered crucial in the development of these conditions. Some studies have even suggested that the level of a person's country of residence may impact the frequency of these symptoms [1-3].

The neurohumoral brain-bowel axis is presented in **Figure 1**.

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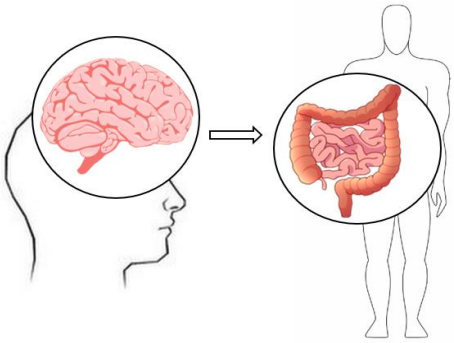

Figure 1. Neurohumoral brain-bowel axis

The present study aimed to investigate approaches to dealing with gastrointestinal disorders in patients with anxiety.

Results and Discussion

Comorbid anxiety and depression in patients with functional gastrointestinal disorders (FDGT)

Patients with functional gastrointestinal disorders (FDGT) often experience comorbid anxiety and depression. This connection is not only related to the need for medical assistance but may suggest a deeper underlying relationship. Some researchers propose that the high rates of psychiatric disorders in FDGT patients indicate that these gastrointestinal symptoms could be an early manifestation of brain dysfunction or even a result of somatization, where the brain affects the gastrointestinal system. However, the connection is more intricate. Some studies argue that gastrointestinal problems tend to appear before emotional disturbances, highlighting the importance of intestinal issues, immune reactions, and the brain's response to these symptoms. If this hypothesis holds, focusing on treating gastrointestinal dysfunction may not only alleviate FDGT symptoms but also improve comorbid mood disorders, as the gut is more accessible for treatment than the brain itself [4-6].

The influence of emotions on gastrointestinal health

People with various temperaments react differently to challenging life events, such as professional setbacks, unfulfilled goals, or the loss of loved ones. Anger is a natural response, yet uncontrolled anger often underlies numerous mental, psychological, and physical health problems. Persistent anger can lead to depression, sleep issues, and somatic conditions. Anger can be categorized into situational anger (triggered by specific events) and characteristic anger (a trait that predisposes individuals to frequent anger) [7, 8].

A study using the Anger Inventory-2 (STAXI) found that people with irritable bowel syndrome (IBS) displayed higher levels of anger, suggesting a link between anger and gastrointestinal symptoms. Further research indicates that patients with functional dyspepsia (FD) tend to exhibit heightened levels of depression, anxiety, and anger. When comparing IBS patients to those with Crohn's disease, the STAXI questionnaire revealed that depression and characteristic anger were more pronounced in those with IBS. Previous studies highlight the importance of addressing anger as a personality trait in treating FDGT. In recent studies, female FDGT patients were found to have higher levels of anxiety, which supports earlier research on the increased prevalence of anxiety and depression in this group. Individuals with FDGT also show more pronounced mental health challenges compared to those without the disorder. The chronic nature of FDGT, which often reduces activity levels and complicates daily life, contributes to greater anxiety and depression. However, unresolved stress and depression may also worsen FDGT symptoms. The question remains whether heightened anxiety and depression in FDGT patients are a cause or consequence of the gastrointestinal disorder [9-12].

Dietary influence on functional gastrointestinal disorders (FDGT)

While psychoemotional factors and gut-brain interaction are recognized as key contributors to FDGT, the impact of diet should not be underestimated [13]. Many patients report a connection between specific foods and the onset of FDGT symptoms, although such associations have not been consistently confirmed in controlled studies. That said, dietary habits can affect the gut microbiome, which may, in turn, contribute to FDGT symptom development. Research indicates that foods containing fermentable oligo-, mono- and disaccharides, and polyols (FODMAPs)—such as certain fruits, legumes, lactose-containing dairy, and artificial sweeteners—can aggravate symptoms due to their fermentation and osmotic properties. Imaging studies show that when FODMAPs are consumed by healthy individuals, the small intestine expands from increased water content [14]. While healthy subjects may not experience symptoms, individuals with FDGT and altered gut sensitivity can develop symptoms upon consuming these

foods. Another noteworthy consideration is gluten sensitivity in the absence of celiac disease. Some patients with irritable bowel syndrome (IBS) and functional dyspepsia, despite lacking celiac markers, report notable symptom relief after eliminating gluten from their diets [15, 16]. The general approach to treating FDGT in individuals with anxiety disorders is summarized in **Table 1**.

Table 1. Fundamental treatment approaches for functional gastrointestinal disorders in anxiety disorders

Treatment approach	Description
Dietary therapy	Eating habits can influence the gut microbiome, affecting gastrointestinal health.
Medical treatment	Central neuromodulators are used to address dysfunctions in the gut-brain axis, which is the biological basis for FDGT symptoms in anxiety disorders.
Augmentation therapy	A combination of neuromodulator treatment and behavioral interventions, such as hypnosis or cognitive psychotherapy, along with the use of tricyclic antidepressants or selective serotonin reuptake inhibitors (SSRIs), especially if there is a pain component. In some cases, a low-dose combination of tricyclic antidepressants and SSRIs may be beneficial.
Cognitive behavioral psychotherapy	Recommended if lifestyle changes, diet modifications, and pharmacotherapy do not show effectiveness after nine months.
Symptomatic therapy	Focuses on alleviating specific symptoms associated with the disorder.

Central neuromodulators, which include antidepressants, antipsychotics, and other medications targeting the central nervous system, are increasingly being prescribed to treat functional gastrointestinal disorders (FDGT). These conditions are now recognized as stemming from disturbances in the relationship between the brain and the gastrointestinal tract. The biological basis for FDGT is linked to dysfunction in the gut-brain axis, the bidirectional neurohumoral connection between the gastrointestinal system and the central nervous system. This connection has a shared embryonic origin, with the neural tube developing into the brain and spinal cord, and sending ganglia to form the enteric nervous system. Both the brain and intestines share the same neurotransmitters and receptors, with their effects varying depending on the location. For example, elevated serotonin can alleviate depression but can also cause diarrhea [17-19].

This understanding supports the use of antidepressants and neuroleptics for treating both mental health issues and chronic gastrointestinal symptoms. In addition to their central effects, these medications can influence the peripheral gastrointestinal system by enhancing serotonin and norepinephrine neurotransmission, potentially explaining some of the benefits of FDGT. Therefore, using central neuromodulators in FDGT patients is justified due to their effects on the gastrointestinal tract [20, 21].

Antidepressants

Tricyclic antidepressants (TCAs)

Tricyclic antidepressants are distinguished by their ability to inhibit both serotonin (5-HT) and norepinephrine reuptake, which makes them more effective at providing pain relief compared to other antidepressants that only impact one neurotransmitter system, like selective serotonin reuptake inhibitors (SSRIs). However, this dual effect can increase the risk of side effects related to heightened serotonin and norepinephrine levels. Most tricyclic antidepressants also have an affinity for other receptors. For example, antagonism of 5-HT2A and 5-HT2C receptors may enhance antidepressant and pain-relieving properties. On the other hand, blocking muscarinic receptors can lead to typical anticholinergic side effects, such as dry mouth, constipation, drowsiness, and blurred vision, while blocking α1-adrenergic receptors can result in dizziness, drowsiness, and orthostatic hypotension [22-26]. Some of these side effects may be beneficial in treating FDGT. For example, anticholinergic effects may help slow down intestinal transit in patients with irritable bowel syndrome (IBS) that is characterized by diarrhea, while increased appetite and weight gain may help patients with functional dyspepsia who experience early fullness and weight loss [24, 27, 28].

Serotonin and norepinephrine reuptake inhibitors (SNRIs)

SNRIs, like tricyclic antidepressants, block the reuptake of serotonin (5-HT) and norepinephrine, thus enhancing their neurotransmission. However, the degree of inhibition varies among the drugs. Venlafaxine, for instance, primarily inhibits norepinephrine reuptake at doses above 225 mg, while duloxetine affects both

serotonin and norepinephrine even at lower doses. Milnacipran strongly inhibits norepinephrine reuptake. Compared to tricyclic antidepressants, SNRIs tend to have fewer side effects, as they do not target other receptors as tricyclics do. Yet, side effects like nausea with duloxetine or increased blood pressure with venlafaxine can still occur. These medications are particularly useful in managing chronic somatic symptoms like neuropathic pain, often seen alongside gastrointestinal disorders [29-31].

In treating irritable bowel syndrome (IBS), tricyclic antidepressants like amitriptyline and imipramine are used as first-line treatments, as they help reduce diarrhea and improve sleep. For patients seeking fewer side effects, desipramine and nortriptyline may be preferred. SNRIs, on the other hand, can improve overall well-being with fewer adverse effects and are particularly helpful for IBS patients with anxiety, especially when abdominal pain or diarrhea isn't the primary concern [29, 32, 33].

Antispasmodics

Guanylate cyclase-c receptor agonists

A newer class of drugs, guanylate cyclase-C receptor agonists, works by stimulating the receptor in the intestines, which triggers a chain of intracellular reactions. This leads to the production of cyclic guanosine monophosphate (cGMP), which enhances the conduction of pain-sensing neurons in the submucosa. This mechanism has been effective in treating pain related to irritable bowel syndrome (IBS). However, the stimulation of cGMP can increase fluid secretion, accelerating intestinal transit, which limits its use in patients with constipation. Linaclotide and plecanatide (both not approved in the Russian Federation) were the first to demonstrate their effectiveness in treating IBS-related pain. Their positive effects typically become noticeable after about two months of treatment [34, 35].

Opioid receptor agonists and antagonists

Visceral m-receptor stimulation is commonly used in the management of chronic diarrhea, including in conditions like irritable bowel syndrome with diarrhea (IBS-D). The development of loperamide, a μ-receptor agonist that doesn’t cross the blood-brain barrier, marked a significant advancement. However, it was noted that several patients experienced increased abdominal pain and constipation with its use. Eluxadoline, a newer treatment (not approved in Russia), works on both μ- and κ-receptors as an agonist and δ-receptors as an antagonist. Animal studies suggest that eluxadoline can decrease visceral hypersensitivity and help regulate bowel movements in IBS-D patients. Eluxadoline has a broader dose range compared to loperamide and doesn’t cause withdrawal symptoms or overdose concerns. Clinical trials with doses of 75 mg and 100 mg twice daily showed improvements in overall well-being, pain relief, and stool normalization within 12-26 weeks. However, the possibility of pancreatitis associated with this drug, especially in patients with liver issues or those who’ve had a cholecystectomy, requires further investigation [36-38].

Serotonin receptor agonists and antagonists

Alosetron, a 5-HT3 receptor antagonist, has been shown to alleviate abdominal pain in women with IBS-D. Although earlier studies noted severe side effects such as constipation and ischemic colitis, subsequent research using smaller doses found minimal complications. A recent prospective study in the U.S. confirmed that a 0.5 mg twice-daily dose of alosetron did not cause major side effects. In Asia, ramosetron, another 5-HT3 antagonist (not available in Russia), is approved for treating IBS-D in both men and women and helps normalize bowel function. Unlike alosetron and ramosetron, ondansetron does not significantly relieve abdominal pain. Prucalopride (marketed as Vegaprate in Russia), a selective 5-HT4 agonist, is primarily used to treat chronic constipation. It works by increasing the frequency of bowel movements and reducing symptoms associated with constipation [39-41].

Augmentation therapy

Augmentation therapy involves combining different treatment approaches when the effects of individual drugs are insufficient. Instead of discontinuing a suboptimal neuromodulator, adding other neuromodulators, often at lower doses, can minimize side effects and provide better therapeutic outcomes. By understanding receptor affinity, the action mode (peripheral or central), and the patient's dominant symptoms, clinicians can select the most appropriate therapy and achieve enhanced effects. While there is no formal evidence supporting the use of augmentation therapy for FDGT, empirical data from depression treatment suggest its potential. Examples include combining neuromodulator treatment with behavioral

interventions (e.g., hypnosis, cognitive psychotherapy), or adding tricyclic antidepressants or selective serotonin reuptake inhibitors, especially when somatic pain is present. In some cases, combining low doses of a tricyclic antidepressant with selective serotonin reuptake inhibitors may also be beneficial [42-44].

Cognitive behavioral psychotherapy

Psychotherapy plays a crucial role in managing FDGT. Techniques such as Cognitive Behavioral Psychotherapy (CBP), interpersonal psychodynamic psychotherapy, and gastrointestinal hypnotherapy have proven effective in treating FDGT, especially irritable bowel syndrome, as shown in meta-analyses. The Russian Gastroenterological Association recommends CBP when lifestyle changes, diet, and pharmacotherapy have been ineffective for nine months. The standard CBP protocol focuses on reducing stress responses to daily life events, while the "interoceptive protocol" helps patients manage anxiety related to visceral symptoms, reducing fear of FDGT symptoms. These protocols assist patients in managing both general and specific anxieties, fostering awareness and trust in their bodies, and improving their disease-oriented behavior. Techniques such as the distress stimulus hierarchy, based on gastrointestinal anxiety triggers (like food or situations), allow patients to control physiological stress through relaxation methods and breathing exercises. Other approaches, such as exposure therapy, mindfulness-based stress reduction, and acceptance and commitment therapy, have also demonstrated effectiveness in reducing both general and gastrointestinal anxiety, alleviating FDGT symptoms, and enhancing the quality of life. Additionally, cognitive behavioral hypnotherapy, which combines CBP and gut-directed hypnotherapy, enables patients to use self-hypnosis to manage gastrointestinal anxiety situationally. Interdisciplinary collaboration among psychiatrists, psychologists, and gastroenterologists is essential for fully addressing the dysregulation of the gastrointestinal tract in these patients [42-46].

Diet, microbiota, and endocrine cells: how they interact

Our diet plays a significant role in shaping the bacteria in our gut, acting as a source of nourishment for them. The composition of our intestinal microbiota is influenced by the foods we eat, which directly impacts the fermentation processes occurring in the gut. Intestinal bacteria ferment food remnants into compounds like methane, hydrogen, and short-chain fatty acids.

While our bodies are equipped to break down starches and glycogen into glucose, we lack the enzymes necessary to break down certain carbohydrates such as fructans and galactans, which are commonly found in foods. Only a small portion of these carbohydrates is absorbed in the small intestine, with the rest traveling to the colon. This can lead to symptoms such as bloating, abdominal pain, and diarrhea, especially in individuals with conditions like irritable bowel syndrome (IBS) [45, 47, 48].

Common foods such as legumes, cabbage, root vegetables, nuts, and flour contain high levels of fructans and galactans, which bacteria in the gut use as fuel. However, these substances can disturb the balance of gut flora, particularly in IBS patients, who often have lower levels of beneficial bifidobacteria. Additionally, a low-FODMAP diet, which reduces the intake of certain carbohydrates, has been shown to reduce the number of butyrate-producing bacteria in the gut.

Research has also highlighted that IBS patients tend to have fewer endocrine cells in their intestines compared to healthy individuals. This lower density of endocrine cells could be linked to a shortage of stem cells or a failure in their proper differentiation [46-49].

Interventions like a low-FODMAP diet and fecal microbiota transplantation (FMT) have been shown to positively impact gut health. These treatments help restore the density of intestinal endocrine cells and improve symptoms. FMT, in particular, can be an effective option for patients who don't respond well to dietary changes, helping to rebalance gut bacteria and improve overall digestive health [47-49].

Conclusion

FDGT, now more commonly referred to as DGBI (disorders of gut-brain interaction), is a condition that remains challenging to treat with conventional methods, primarily due to the limited effectiveness of pharmacological treatments. However, emerging research highlights the growing significance of these therapies. Several treatment approaches have been identified that can address multiple aspects of this complex condition.

The interaction between the gut and the brain is increasingly recognized as central to understanding DGBI, emphasizing its importance for treatment

strategies. For mild intermittent symptoms (e.g., worsening after eating or relief after defecating), peripheral neuromodulators are typically effective. However, as the condition becomes more chronic and symptoms intensify—such as abdominal pain, nausea, vomiting, and extra-intestinal symptoms—adding central neuromodulators to the treatment regimen should be considered.

Moreover, the personal characteristics of each patient with DGBI are crucial to treatment success. Therefore, a biopsychosocial treatment approach is recommended, combining pharmacotherapy with cognitive behavioral therapy. This integrated strategy offers the best chance for effectively managing the condition and improving the patient's quality of life.

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