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THE EFFECTIVENESS OF PHARMACOLOGICAL, DIETARY, PSYCHOLOGICAL AND NOVEL TREATMENTS IN IRRITABLE BOWEL SYNDROME

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ABSTRACT

Research objectives: Irritable bowel syndrome (IBS) is a functional disorder of the gastrointestinal tract with a complex pathogenesis in which the brain-gut axis is disrupted. Due to the multifactorial basis of the disorder, it is very important to combine pharmacological and psychological treatment with dietary treatment to alleviate patients' symptoms.
The purpose of this dissertation was to present the effectiveness of pharmacological, dietary, psychological and novel treatments currently at research level in patients with irritable bowel syndrome.
Method: In order to evaluate the effectiveness of various therapies in IBS, a systematic review was conducted. It covers articles from years 2020 - 2024, that were published in PubMed, MDPI, and Sage Journals databases.
Key Findings: The treatment of irritable bowel syndrome requires a combination of different therapies to achieve an effective therapeutic effect. There is no specific form of treatment to cure IBS.
Conclusions: Currently it is only possible to alleviate the discomfort and improve the quality of life by combining the various methods available. The method that seems to be the most effective is a combination of pharmacological, dietary and psychological treatment. Pharmacological therapy makes it possible to alleviate pain, constipation or diarrhea. The introduction of the FODMAP diet eliminates factors that adversely affect the intestinal microbiota, and psychotherapy, combined with pharmacological treatment of depression and anxiety, alters thinking and synthesizes hormones that affect the gut-brain axis. Alternative treatments are currently being researched, but it will take time and further research before these methods can be incorporated into standard therapy.

KEYWORDS

Irritable Bowel Syndrome, Treatment, Probiotics, Fecal Microbiota Transplantation, Psychotherapy

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1. Introduction

Irritable bowel syndrome is a functional disorder of the gastrointestinal tract that chronically impairs its proper functioning and reduces overall quality of life, affecting 9-23% of the population. [1] It is most commonly manifested by recurrent abdominal pain, diarrhea, constipation, bloating and abnormal bowel movements. The pathogenesis is multifactorial and not fully understood, with disorders of the brain-gut axis, visceral hypersensitivity, abnormal composition of the intestinal microbiota and psychiatric disorders considered as the most important. Due to the uncertain pathogenesis of the disease, treatment is mainly symptomatic and focuses on soothing patients' symptoms.

The diagnosis is established on the basis of typical symptoms reported by the patient; physical examination, exclusion of other causes that may cause similar symptoms, and after finding no abnormalities in basic diagnostic tests. According to the Rome IV criteria, we can distinguish four forms of IBS depending on the main pattern of bowel movements: with diarrhea, with constipation, mixed and unspecified [2].

In addition to intestinal symptoms, patients have extra-intestinal symptoms, probably up to 40-60% of patients may suffer from psychiatric disorders among which depression and anxiety predominate. When choosing a treatment for irritable bowel syndrome, the type of disease and the main accompanying symptoms should be taken into account. [3]

1.2 Pathogenesis of irritable bowel syndrome

Abnormal peristalsis and abnormal work of the colon are salient factors in the pathophysiology of IBS. [4] The main symptoms in patients are recurrent abdominal discomfort, abdominal pain and altered bowel movements. Clinical studies on the pathogenesis show that the causes of these complaints are mainly the microbiome, endocrine cells of the gastrointestinal tract, visceral hypersensitivity and gastrointestinal motility disorders. [5] There is also a growing body of research on the epigenetic etiology of IBS. Recent studies have demonstrated that enterocytes of the intestinal crypts are key cells in host-microbiome interactions that contain both histone modifications and miRNA signaling. [6] The analysis of stool samples, colon biopsies, duodenal aspirates or breath testing are used to examine the gut microbiota. [7] The constipated form of IBS is caused by the impaired excretion of food contents from the colon. Rectal manometry is performed for diagnosis.[4] The pathomechanism of diarrhea in IBS is based on mutations in the jejunal epithelial barrier gene saccharose-isomaltase and abnormalities in the production of proteins involved in digestion and metabolism, especially after ingestion of fatty and proteinaceous foods, as well as fermentable carbohydrates. [8]

One in four patients with the diarrheal form of IBS has idiopathic bile acid diarrhea. The primary bile acids: chenodeoxycholic acid and cholic acid which pass into the small intestine after ingestion of a meal and contraction of the gallbladder, then undergo transformation in the colon to secondary bile acids, where they cause increased mucosal permeability and stimulate muscle motility. Patients with bile acid diarrhea have increased levels of fasting serum alpha-hydroxy-4 cholesterol-3-one (7αC4), an indirect marker of bile acid synthesis in the liver. [4]

2.Pharmacological treatment

2.1 A popular drug for IBS-D is **loperamide**, an opioid agent, used to relieve diarrhea. However, its effect on improving abdominal discomfort has not been proven, [5] moreover, the use of loperamide is associated with side effects such as nausea, cramping and constipation. [9] Another drug that relieves symptoms of both pain and diarrhea are **eluxadoline** (an opioid agent), **rifaximin**, an anti-inflammatory antibiotic, and **aldosetron** (5-HT3), which delays intestinal transit and has the proven effective in reducing visceral pain. [5]

Rifaximin is a non-systemic antibiotic that is slightly absorbed from the gastrointestinal tract. Compared to placebo, it significantly alleviates IBS symptoms such as bloating. 2-week antibiotic treatments are well tolerated by patients, and although the mechanism of action of rifaximin has not been completely elucidated, studies suggest its beneficial effects on stabilizing the intestinal microbiota, reducing inflammation, visceral hypersensitivity and intestinal wall permeability. [10] Although rifaximin showed to be more beneficial than placebo, there was a gradual reduction in the percentage of patients with relief of IBS symptoms. In most patients, IBS symptoms recur despite rifaximin therapy, and its efficacy and safety remain questionable. Neomycin is another antibiotic that was tested for the first time in IBS therapy. The symptom relief was observed, yet neomycin is not used due to its ototoxicity. [7]

2.2 Agents that increase stool volume and exhibit osmotic laxative effects are recommended in the pharmacological treatment of IBS-C. A highly effective drug that increases osmotic secretion is **linaclotide**. **Lubiprostone** and **plecanatide** are moderately effective. These are increasing Cl- and water secretion, **tenapanor** (an NHE3 inhibitor), which stimulates Na+ and water secretion, and **tegaserod**. [5]

2.3 Diastolic medications: anticholinergics and drugs that inhibit the influx of calcium into smooth muscle cells are used to relieve abdominal pain. Both of them successfully affect pain and improve bowel frequency. [5] Anticholinergic drugs that are commonly used also include **dicyclomine**, but its use might with numerous side effects due to muscarinic receptor blockade and acetylcholine inhibition, such as constipation, urinary retention, visual disturbances and dry mouth. **Peppermint oil**, **pinaverine** and **trimebutine** are also frequently used.[5] [7].

While discussing the gastrointestinal tract, **pinaverine bromide** exhibits spasmolytic effects in two ways. As a selective antagonist of calcium channels, it blocks the influx of calcium into smooth muscle cells and, in addition, reduces the contractile effects of inflammatory mediators and digestive hormones. Furthermore, pinaverin bromide reduces abdominal pain and abdominal discomfort. Patients taking pinaverin experienced a reduction in IBS symptoms compared to those taking placebo. [11]

2.4 Central neuromodulators affecting transmitters such as serotonin, norepinephrine and dopamine are used to treat pain in IBS patients.

Tricyclic antidepressants (**TLCs**) are used as first-line medications. These include amitriptyline, imipramine, desipramine, nortriptyline.

Serotonin-norepinephrine reuptake inhibitors (**SNRIs**) are used as second-line drugs when TLCs are poorly tolerated or ineffective. They are particularly indicated in patients with comorbid depression and when diarrhea predominates in the patient's IBS picture. These include duloxetine, venlafaxine and milnacipran as an alternative used in the US.

Another drug showing efficacy in the treatment of IBS is **mirtazapine**, a quaternary antidepressant, which in preliminary studies had an effect on relieving abdominal cramps and reducing the sensation of abdominal pain. In addition, there was an improvement in quality of life and a reduction in feelings of anxiety in the group of patients taking mirtazapine compared to those receiving placebo. [12]

3. Dietary treatment

Dietary treatment is an extremely important part of IBS treatment. The effectiveness of the diet is greater in patients who consume an adequate amount of calories than in patients whose energy intake is lower.[13] In addition, due to the occurrence of diarrhea in people with IBS, it is very important to have a well-balanced diet to ensure not only an adequate supply of kilocalories, but also of macro- and micronutrients. Intestinal malabsorption and chronic inflammation can lead to, among other things, iron deficiency, fatigue and increased susceptibility to infection. [14]

3.1 The traditional IBS diet - the NICE diet and therefore a diet based on three meals and three snacks, in which meals are small and of similar size. Patients should avoid situations of feeling hungry and overeating. Meals should be eaten peacefully, in a quiet place [13]. Coffee, alcohol, sweeteners, spicy and fatty foods should be eliminated from the diet, but foods high in FODMAP are not excluded. This type of diet is suggested at the beginning of the introduction of dietary interventions and is effective in patients with higher baseline oligosaccharide intake.The introduction of a FODMAP diet is recommended especially when there is no symptom’s relief in the previous treatments. [15]

3.2 The FODMAP diet is based on the elimination of products containing high amounts of fructans (e.g. wheat, onions, garlic), oligosaccharides (e.g. legumes), lactose (e.g. milk), fructose (e.g. apples) and polyols (e.g. sweeteners). Foods high in FODMAPs, or fermentable carbohydrates, are poorly absorbed from the small intestine, and unabsorbed lactose, fructose and polyols, through their osmotic effects, increase the amount of water in the small intestine [16]. These move to the large intestine undigested and unabsorbed, where they are fermenting, resulting in an excessive production of gases responsible for the occurrence of bloating. [17] The FODMAP diet consists of three phases: elimination (that lasts 4 - 6 weeks), reintroduction and personalized. [18] After the elimination of highly fermentable foods, a patient gradually introduces them into the diet, based on the patient's individual tolerance. The ultimate goal is to use the diet as a long-term solution, so it has to be not only accepted by the patient but also provide all the necessary nutrients [1] It is a second-choice diet, used when there is no improvement after the introduction of the IBS diet. The introduction of a FODMAP diet, in patients with a high baseline intake of FODMAP products, has worse results than the introduction of an IBS diet. On the other hand, in patients with a more pathogenic composition of the intestinal microbiota, the FODMAP diet has better results than the IBS diet. However, it is important to note that the choice of diet should be discussed individually and patient-tailored, as both the traditional IBS diet and the FODMAP diet have satisfactory results and symptom reduction. [15]

3.3 Probiotics are live microorganisms, strains of bacteria or yeast that naturally occur in the intestines of humans and animals and in certain foods. In healthy people, the richness of the gut microbiota is high, while in IBS patients the diversity of the gut microbiota is lower. It led to numerous studies being conducted on the effect of probiotics on increasing the diversity of the gut microbiota in IBS patients and reducing the sensation of symptoms. Due to differences in age, gender, type of IBS and the diversity of the gut flora of individual patients, it is generally difficult to determine the effectiveness of the probiotics used.[13] The terms microbiome and microbiota are often used interchangeably, but are strictly different. The microbiota refers to a collection of microorganisms (e.g., bacteria, viruses) living in a specific environment, while the microbiome includes the entire ecological community, or microbiota, and their structural elements, such as proteins, lipids and genetic material, microbial metabolites such as signaling molecules or toxins, and the environmental conditions in which they coexist. [7]

According to studies, the mixture of Lactobacillus rhamnosus and Lactobacillus acidophilus is proven to be most successful. It reduces pain sensation and improves the quality of life of patients, reducing bloating, intestinal cramps and the feeling of overflow. The combination of Lactobacillus rhamnosus and Bifidobacterium animalis subsp. lactis has shown great effectiveness in relieving constipation, reducing the feeling of overflow in the intestines, reducing the sensation of pain and abdominal bloating. The combination of the three strains mentioned above is the least effective but showed promising results in reducing intestinal cramping. [19] Probiotics, as generally effective, safe, well-tolerated and relatively inexpensive, are recommended for the treatment of patients with IBS, but their efficacy requires further research. [13]

3.4 Many synthetic drugs are analogs of plant metabolites with proven effectiveness against IBS. These include resveratrol, soy isoflavones, curcumin, fennel, cumin and peppermint. Terminalia Chebula is an interesting discovery - it shows multidirectional effects: anti-anxiety, antidepressant, sedative-sleep and antioxidant. This remedy improves digestion and relieves constipation, reduces intestinal spasms, relieves visceral pain, and additionally regulates the intestinal microbiota. [9]

4. Physical exertion

According to the WHO, every adult without health contraindications should exercise 150-300 minutes per week of moderate-intensity activity or 75-150 minutes of high-intensity aerobic activity. [20] Regular physical activity improves overall fitness, contributes to an improved quality of life and reduces the severity of constipation. In addition, exercise helps reduce body weight which might be important as numerous studies have shown that the incidence of IBS is three times higher in obese patients compared to normal weight patients. [21] The exact mechanism by which physical activity reduces the incidence of IBS symptoms is not known, but studies have shown that it prevents the accumulation of gases in the intestines and accelerates their elimination from the body, thus its effect is prokinetic. In addition, it improves the mood of patients, reduces symptoms of anxiety and depression, and has a positive effect on the functioning of the nervous system. The positive effect of physical activity on the alleviation of IBS symptoms was observed in patients of all age groups, and some patients, due to the introduction of regular physical activity, reduced the doses of medications used to alleviate symptoms. The most preferred form of activity was walking, but in each case the type and duration of activity should be determined according to the patient's ability. [20]

5. Psychological treatment

IBS patients living under greater psychological stress have a worse response to dietary treatment, especially when compared to patients with lower levels of stress. Behavioral therapy, mainly focused on the brain-gut axis, puts an emphasis on remediating the psychological and cognitive factors that influence the perception of gastrointestinal symptoms, primarily anxiety, and a sense of lack of control over one's bowels. Therapies that have been most tested in the context of IBS include cognitive-behavioral therapy, gut-focused hypnotherapy, interpersonal psychodynamic therapy and various forms of relaxation. [22]

5.1 Cognitive-behavioral therapy is one of the most effective forms of psychotherapy used for patients with IBS. [23] It focuses on eliminating maladaptive thoughts that negatively affect the patient's behavior and experiences. [24] The exact mechanism by which it exerts a positive effect on reducing the symptoms experienced by patients is unknown. It is likely that it convinces patients to change their way of thinking which induces the synthesis and release of hormones that affect the brain-gut axis. As an effect, it alters patient behavior, including their dietary choices. Studies have shown that it improves patients' quality of life, relieves somatic symptoms such as diarrhea, constipation and bloating, and reduces the fear of food and visceral distress characteristic of these patients. In addition, it affects changes in the intestinal microbiota by increasing Roseburia , Lachnobacterium and Lachnospiraceae, and decreasing Bacteroides, Parabacteroides and Prevotella. [23]

5.2 Mindfulness therapy is a long-term technique that reduces the severity of patients' somatic symptoms, improves quality of life and modifies psychiatric symptoms such as depression, anxiety and anger. The therapy is associated with increased optimism, improved life satisfaction, greater self-confidence and belief in success. [23]

5.3 As one of the methods of psychotherapy, **hypnotherapy** allows patients to reduce the severity of their symptoms as early as six months after the start. Nonetheless, the greatest effectiveness is observed after three months of hypnotherapy. Studies have indicated that patients with more severe forms of IBS were more amenable to hypnotherapy compared to patients with a milder course of the disease [25]. Hypnotherapy significantly improves psychiatric symptoms, reduces feelings of anxiety and the severity of depressive symptoms. Patients undergoing hypnotherapy twelve months after its initiation reported fewer problems at work and greater productivity. Fewer absences from work due to IBS symptoms were also reported when compared to patients not receiving hypnotherapy.

Both individual and group hypnotherapy resulted in less bloating, a reduction in the frequency of abdominal pain, and a reduction in the severity of anxiety. Unfortunately, the quality of life did not change in patients undergoing group hypnotherapy. [23]

6. Other treatments

6.1 Fecal microbiota transplantation (FMT) is the transplantation of feces from a healthy donor who can be both related and unrelated individuals. Transplantation is performed by endoscopy methods: both gastroscopy and colonoscopy, as well as by capsule, via rectal probe or gastrointestinal probe. Given the changes in the microbiota in patients with IBS, fecal transplantation can help regulate the microbiota in these patients, which may subsequently lead to a reduction in intestinal complaints. [26] Abnormalities in the gut microbiota can affect a patient's brain function and behavior, and are therefore linked to the development of neuropsychiatric disorders such as anxiety and depression. Findings indicate that the composition of the gut microbiota of healthy people differs from that of people suffering from depression. [27] FMT is a safe method in patients with typical IBS symptoms, but unfortunately, its effectiveness is comparable to placebo. There are scientific evidences suggesting that FMT may have a beneficial effect on symptom relief in IBS patients, but further scientific research is needed.[26]

6.2 Transcutaneous vagus nerve stimulation is not currently used as a treatment option for patients with IBS, however, the results of studies show that it reduces paracellular permeability of the intestines in patients after a single dose of CRH, compared to patients with sham stimulation. Thus, it might be considered as a future treatment option for diseases in which intestinal permeability is increased.[28] Intestinal permeability changes in various life situations, physiologically in stressful situations and pathologically in inflammation and disease. A study was conducted; patients were given a single dose of CRH that posed a stressful situation. Its effects were assessed by changes in plasma I-FABP concentrations and urinary lactulose and mannitol concentrations as a two-sugar test. I-FABP protein is an intracellular protein that is released into the bloodstream when epithelium is damaged. Lactulose and mannitol are the sugars used in the intestinal permeability test, which the subjects were given to drink, diluted in 450ml of water. The concentrations of I-FABP did not differ between the two groups of subjects, increasing for both active and sham stimulation, while the ratio of lactulose to mannitol in the urine was lower for the group after active stimulation compared to sham stimulation. The results of the study indicate that 20 minutes of vagus nerve stimulation reduces paracellular intestinal permeability by more than 50% when compared to sham stimulation. As a result, it may be used in the future as one of the alternative, non-pharmacological methods to alleviate symptoms and treat patients with IBS.[29]

6.3 Acupuncture

Clinical studies examining the efficacy of acupuncture in IBS patients have confirmed the positive effects of this intervention in reducing visceral hypersensitivity and improving abnormal activity of the brain-gut axis. [30]

7. Conclusion

The treatment of irritable bowel syndrome varies widely and depends on a number of factors. These factors include the form and severity of IBS symptoms, age, gender, composition of the intestinal microbiota, concomitant psychiatric disorders or the patient's individual response to the treatment used. The diagnosis of IBS itself requires the exclusion of organic disease through careful history taking, physical examination and a series of diagnostic tests. The choice of therapy should be patient-tailored and take into consideration a specific and unique approach, focusing on the patient's main symptoms, as well as their severity and factors affecting the course of IBS. The doctor must also demonstrate empathy and psychological knowledge without downplaying the patient's complaints, even though these might be considered as exaggerated. [31]

Disclosure
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