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Advances in Irritable Bowel Syndrome: Exploring Novel Therapeutic Strategies

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Abstract: Irritable Bowel Syndrome (IBS) is a functional gastrointestinal disorder characterized by symptoms such as bloating, abdominal pain, and changes in bowel habits. The condition affects a significant portion of the global population, with prevalence higher among females and younger individuals. Despite its widespread impact, IBS remains a complex, multifactorial disorder without a clear pathophysiology. Recent advances have highlighted the roles of diet, stress, the gut-brain axis, microbiota, and genetic factors in IBS. Therapeutic strategies have evolved, encompassing dietary changes, stress management, probiotics, and pharmacological interventions like chloride channel activators and serotonin receptor modulators. Non-pharmacological approaches, including cognitive behavioral therapy (CBT) and regular exercise, are also proving beneficial in improving patients' quality of life. This review focuses n current developments in IBS treatment, emphasizing a holistic, individualized approach to managing this challenging disorder.

Keywords: Irritable Bowel Syndrome (IBS), Diagnosis, Management, Pathophysiology, Treatment, Novel therapeutic advances

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Introduction

A functional gastrointestinal disorder is irritable bowel syndrome (IBS), and the symptoms are bloating, abdominal pain, and changes in bowel habits such as diarrhoea, and constipation. Distension, irregular defecation, and sensation of discomfort (bloating) are commonly linked features. It affects a major population, with varying degrees of severity that can affect standard of living (Quigley *et al*., 2016). IBS can affect around 7–10% of the global population, and it varies according to geographical criteria. IBS is a more common disease in females compared to males, the age groups younger than 50, and in lower socioeconomic groups (Scalera and Loguercio, 2012).

Etiology of IBS

IBS has been found to be triggered by lactose intolerance, sorbitol intolerance, or fructose intolerances. It is likely that the cause of IBS is not the deficiency of a specific enzyme but rather that the hypersensitive gut of patients with irritable bowel syndrome (IBS) exaggerates responses to the gaseous and fluid distention caused by incomplete absorption of carbohydrates (Karantanos *et al*., 2010). Both clinical and preclinical studies show that stress has a considerable impact on motility, intestinal sensitivity, permeability, secretion, as well as mucosal immune activation. These changes are mediated by the peripheral neurons, the central nervous system (CNS), and the gastrointestinal microbiota and are linked to stress-related disorders (Raskov *et al*., 2016). The gut-brain axis has been characterized extensively over the last 10 years, and current evidence indicates that there are multiple pathways through which microbiota to brain signaling, including endocrine and neurocranial pathways, and that the brain is also capable of modulating the microbial community and mental behavior using the ANS (Chey *et al*., 2015).

Pathophysiology of Irritable Bowel Syndrome (*IBS*)

Small bowel motility problems like Stress, meals, and cause stronger motor responses than normal. Discrete cluster contractions happen more often and last longer. Migrating motor complexes and backward contractions occur more. Abnormalities in colonic motility include increased motor responses to stress, hormones, and meals, reduced postprandial colonic tone, and altered number and propagation of high amplitude contractions. Genetic Predisposition can also cause IBS. Family Aggregation studies suggests that there may be a genetic component to the clustering of cases typically reported within families. Twin Studies indicate heritability. Gene Associations like gene polymorphisms in IL-10, TNF-α and serotonin metabolism have been linked to IBS (Fig. 1). Gene-Environment Interactions are involved in onset of the illness. A common finding in patients with irritable bowel syndrome (IBS) is visceral hypersensitivity. It is caused by different factors such as central nervous system and peripheral nervous system. Afferent nerves carry visceral sensations from the GI Tract to the brain and spinal cord, where pain and discomfort are perceived. These signals can be intensified at a different points (gut, spinal cord or brain) leading to notable increase in the brain response observed in IBS patient (Gasbarrini *et al*., 2008). Bloating is extremely prevalent in the patients of IBS. Patients with IBS-C experience bloating more frequently than those with IBS-D, and bloating in IBS-C patients is associated with abdominal distension. There is no proof that there is an increased amount of gas within the intestine leading to bloating (Barbara *et al*., 2013). It has been observed that stress, anxiety, depression, phobias and somatization are linked with the expression and progression of IBS (Barbara *et al*., 2004). Inflammatory disease has been observed in many patients who have a symptom of IBS. After the inflammatory response some changes exist in the intestinal permeability and infiltration of the inflammatory cells that leads to the localized oedema and subsequently cytokines which may probably in association with the neuromuscular dysfunction and altered peristalsis leads to the symptoms of IBS. In IBS patients increased amounts of interleukin-6, tumour necrosis factor-α, interleukin-10 and other cytokines, and their concentration is linked with the severity of pain and frequency, but also with anxiety (Hadjivasilis *et al*., 2019).

Pathological changes in IBS

The gut bacterial composition in IBS patients is significantly different from that of healthy individuals. Patients with IBS typically have reduced levels of butyrate-producing bacteria, such as Ruminococcaceae and Erysipelotrichaceae, compared to non-diseased individuals. Methano-bacteriales, the bacteria that produce methane, are more prevalent in IBS patients who have constipation (IBS-C) and less prevalent in those who have diarrhea (IBS-D) than in healthy individuals. Overall, IBS patients tend to have

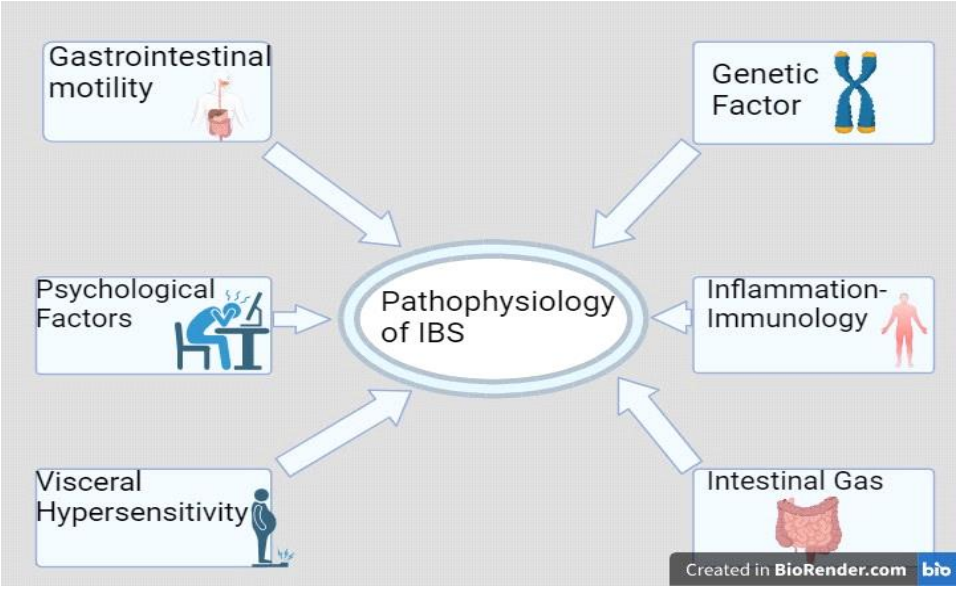

Fig. 1: Pathophysiology of IBS (Chong *et al*., 2019).

lower gut bacterial diversity, indicative of dysbiosis (Gasbarrini *et al*., 2008). The relationship between irritable bowel syndrome (IBS) and small intestinal bacterial overgrowth (SIBO) is complex. IBS patients may have abnormal breath hydrogen levels after ingesting carbohydrates, and their symptoms can improve with treatment for bacterial overgrowth. Additionally, higher methane production by intestinal bacteria has been linked with constipation-predominant IBS. However, although IBS patients had slightly higher bacterial counts, this was not linked to symptoms or intestinal motility (Karantanos *et al*., 2010). IBS patients have increased numbers of chronic inflammatory cells in the lining of their colon. The lamina propria, as well as the surface and crypt epithelium of IBS patients, have higher concentrations of T lymphocytes. In addition, nearly 90% of IBS patients have a significant rise in CD25-expressing lamina propria inflammatory cells, a marker of immune activation (Kirsch and Riddell, 2006). Hiatt and Katz (1962) observed more mast cells in the muscular layer of the colon in spastic colitis patients, further research was limited due to difficulties in obtaining full-thickness colon samples. Higher mast cell density was also seen in the cecal mucosa of IBS patients. Newer research using advanced methods like electron microscopy and immunohistochemistry revealed a higher density of mast cells in the cecum, descending colon, and rectum. Ultra-structural analysis revealed more degranulating mast cells and an increased concentration of mast cells near enteric nerves in various parts of the colon (Kirsch and Riddell, 2006). Patients with post-infectious IBS (PI-IBS) had higher numbers of enterochromaffin cells (EC) in their rectal biopsies, but not in those with non-post-infectious IBS. Two weeks after a *Campylobacter jejuni* (Spiller *et al*., 2000) infection, there was a fivefold increase in EC cells, characterized by synapto-physin positivity (Kirsch and Riddell, 2006). In biopsies from the rectosigmoid and terminal ileum of both post-infectious and non-post-infectious IBS patients, there is an increase in nerve fibers that test positive for markers such as 5-HT, substance P, and neurone-specific enolase. IBS patients have a reduced distance between their enteric nerve fibers and inflammatory cells like mast cells and lymphocytes (Kirsch and Riddell, 2006).

Classification of IBS

Based on Rome III criteria, Irritable Bowel Syndrome (IBS) can be classified into four types:

IBS-D (IBS with diarrhoea), IBS-C (IBS with constipation), IBS-M (IBS with diarrhoea and constipation), and IBS-U (IBS with undefined symptoms). IBS-D, also known as diarrhoea-predominant IBS, occurs on days when the person has at least abnormal bowel movement, with more than a 1/4th of the stools being loose or watery and less than a 1/4th of the stools being hard or lumpy. IBS-C, also known as cnstipation-predominant IBS, occurs on days when the person has at least abnormal bowel movement, with more than a 1/4th of the stools being hard or lumpy and less than a 1/4th of the stools being loose or watery. IBS-M, also called an alternating type of IBS, occurs on days when the person has at least abnormal bowel movement, with more than a 1/4th of the stools being hard or lumpy and more than a 1/4th of the stools being loose or watery. In IBS-U, the symptoms are undefined in this lack of substantial abnormalities of stool consistency to meet criteria for IBS-D, IBS-C, or IBS-M. (Grad and Dumitrascu, 2020).

Diagnosis of IBS

The IBS authorities and Rome committee recommend various tests for diagnosing IBS (Table 1). These includes Blood test, Stool test, Hydrogen breath testing, Clinical history, Testing for bile acid malabsorption, and Biomarkers in IBS. The future newer innovative tests for IBS.Several studies have looked at using blood tests, like serum chemistries, thyroid function tests and complete blood test (CBC), to diagnose suspected IBS (Table 1). Testing for celiac disease in suspected IBS patients showed that they had a higher prevalence of celiac disease compared to controls. Blood tests should be personalized based on the patient's specific symptoms, severity, and concerns (Cash and Chey, 2004). Tolliver *et al*. (1994) looked at using fecal occult blood tests (FOBT) for patients suspected of having IBS. A complete colonoscopy was performed on 183 individuals (8.2%) who had a positive FOBT. Structural abnormalities discovered during the colonoscopy were discovered in four of these fifteen individuals, or 2.2% of the original group. However, none of these abnormalities explained the patients' IBS symptoms or suggested a different diagnosis. Stool tests for parasites and ova are often recommended for suspected IBS patients. (Cash and Chey, 2004). Lactose malabsorption can be diagnosed through hydrogen breath testing. However, a lactose-free diet helps with IBS symptoms is unclear. IBS symptoms are frequently associated with small intestine bacterial overgrowth (SIBO) (Cash and Chey, 2004). The clinical history is necessary to accurately diagnose IBS. It helps to rule out other gastrointestinal diseases and to determine the IBS subtypes using the Bristol Stool Form Scale (BSFS) (Lewis and Heaton, 1997). The BSFS is a stable marker for water content and transit time and is the basis of Rome IV criteria IBS subtypes (Goldstein and Cash, 2021). Bile acid malabsorption is a well-known cause of chronic diarrhea, and commonly seen in IBS-D particularly the diarrhea-predominant type. Studies show that selenium-homocholic acid taurine (SeHCAT) testing indicates that BAM may be present in 25-33% of patients with IBS-D. The SeHCAT test is the most reliable and most frequently used test for diagnosing BAM. When the retention value falls below 10% then the BAM is diagnosed. The SeHCAT test is accurate and readily available, although BAM is still under-diagnosed, partly because of its exclusion from differential diagnoses for chronic diarrhea, and/or difficulty diagnosing the condition (Kurien *et al*., 2011). Currently it is not possible to identify IBS or recommend specific disease markers for the routine diagnosis of IBS (Soares, 2014). In the United States, a blood screening test called Prometheus® IBS diagnostics has been approved for patients diagnosed with IBS (Suares and Ford, 2011). This test is a part of a set of 10 "IBS blood biomarkers" that can be used to confirm the diagnosis of IBS when combined with other clinical parameters. Definitive evidence of patients with IBS by means specific "disease markers" is not possible currently and is not currently recommended for the routine clinical diagnosis (Soares, 2014).

Table 1: Symptom-Based diagnostic criteria for IBS (Weaver *et al*., 2017)

Characteristic	Rome III	Rome IV
Diagnosis duration	•Symptoms appear at least six months earlier. •Symptoms happened at least three days per months. •Symptoms stayed active in the past three months.	•Symptoms appear for a minimum of six months earlier. •Symptoms happened at least one days each week •Symptoms stayed active in the past three months
Symptom description	Pain in abdomen	Pain in abdomen
Association of symptoms (2 or more)	•Defecation improvement •Symptoms begin with change in the shape of stool •Symptoms begin with an alteration in stool frequency.	•Symptoms are assosiated with defecation •Symptoms are associated with alteration in the stool form •Symptoms are associated with the alterations in the stool frequency.
IBS subtype (IBS-C, IBS-D, IBS-M, and IBS-U) predominant stool pattern	Type of stool based on bowel movements per day.	Type of stool based on days with irregular bowel movements.
Tool for categorizing the bowel habit	Bristol Stool Form Scale	Bristol Stool Form Scale.

Management of IBS

The physician and patient should develop a trusting relationship for the management of IBS patients (Chey *et al*., 2015). It is largely accepted that physical exercise plays a major role in maintaining good physical, mental and social well-being. By doing the exercise regularly, it reduces the intestinal gas problem, bloating, constipation, and increases gut microbial diversity (Black and Ford, 2021). A study on IBS patients and healthy individuals shows that physical exercise protects against gastrointestinal symptoms and increases the colonic transit time (Ford *et al*., 2018). Gastroenterologists suggest physical exercise like yoga, Taiji, aerobic exercise and mountaineering to maintain physical fitness and reduce the symptoms of IBS (Pietrzak *et al*., 2018). It plays a major role in the management of IBS. Lifestyle and dietary changes may be the initial line of treatment for many patients with IBS, relieving their symptoms without the need for additional treatment. It encourages healthy eating habits and increases physical activity, and IBS patients do not intake caffeine, fat, alcohol, spicy food and gas producing food (Moayyedi *et al*., 2017). The fermentable, oligosaccharides, disaccharides, monosaccharides and polyols (FODMAPs) was developed by the British Dietetic Association and certified by National Institute for Health and Care Excellence (NICE) that aids patients with easily understandable dietary information. For Foods that are considered to include in the diet of an IBS patients, the gastroenterologists should explain the significance of consuming fruits and vegetables. These meals are full of nutrients and do not include any FODMAPs or other ingredients that might trigger IBS. The presence of glucose in food items containing fructose improves tolerance because glucose enhances absorption of fructose. It reduces the absorption of fructose in the gastrointestinal tract and triggers IBS symptoms (Coutts, 2019). We have to pay much more attention in the treatment of IBS to regulating stress and stress related actions. Non-pharmaco-logical methods are receiving more attention as a result of traditional medications' poor effectiveness in providing the right care, such as laxatives. They should accommodate the relation

between physician and patient, placebo, educating patient, behavioral therapy, use of hypnotherapy, modification in diet it includes exercise, probiotics and biofeedback (Qin *et al*., 2014). A psychologist with strong communication skills and relaxation therapies helps reduce the symptoms of IBS when the patient frequently visits and takes consultation (Gunn *et al*., 2003). At this stage, formal psychiatric or psychological evaluation is more suitable than further gastrointestinal studies (Viera *et al*., 2002). Probiotics, such as *Bifidobacterium* and *Lactobacillus*, are nonpathogenic and help promote digestive health. Probiotics may be of different species or strains, different preparations and doses, bringing difficulties to the available literature on efficacy data (Khan and Chang, 2010). There are still valid enough reasons that do not recommend against trying probiotics, especially combinations for up to twelve weeks, after that combination should be forgotten or treatment discontinued if no more improvement of the symptoms has been suffered (Black and Ford, 2021). Dietary fibers are indigestible carbohydrates, which include resistant starch, cellulose, and glucans, these components are essential structural parts of grains, fruits, vegetables and legumes. Soluble fibers in the GI tract form a gel that interact with gut bacteria, they also tend to quicken GI transit (Pietrzak *et al*., 2018). More specifically, patients suffering from IBS-C need to be advised in sufficient amounts on the intake of a varieties of fiber foods which are partially fermentable and are found in various types of cereals, and if gas-related symptoms is a problem, intake of soluble fibers rather than insoluble fibers seems beneficial (Algera *et al*., 2019). Recommended sources of soluble fibre include vegetables, fresh fruits, plantains (ispaghula, psyllium, *Plantago ovate*, *Plantago lanceolata*), oat bran and supplements which are ready-made (Pietrzak *et al*., 2018). In summary, dietary fibers have a positive effect in the management of IBS patients, especially among IBS-C patients. Dietary fibers are also simple, safe and cost effective as they are usable in greatest variety in various foodstuffs (Algera *et al*., 2019). CBT has been validated as a useful intervention for both the physical and psychological aspects of the disease. CBT focuses on the cognitive behavioral techniques that are used in changing cognitive and behavioral processes related to IBS. Such aspects enable the patients to understand the connections among their ideas, feelings, thoughts, relations and physical symptoms resulting to better management of these symptoms (Lackner *et al*., 2007).

Treatment of IBS

Antidiarrheals: Loperamide is more beneficial than placebo in the allevation of symptoms of diarrhea but not abdominal pain in IBS (Talley, 2003). Loperamide is among the most commonly prescribed drug in the treatment of IBS-D. Loperamide decreases the speed of intestinal peristalsis while enhancing intestinal absorption of water and ions (Hammerle and Surawicz, 2008). Loperamide, could decrease the frequency of bowel movements and the liquidity of the stools and also contributed to the global well-being benefits (Wall *et al*., 2014). Treatment with simethicone in addition to loperamide is better than loperamide alone in acute diarrhoea due to the possible gas trapping effects of simethicone but has not been tried for IBS (Talley, 2003). Other antidiarrheal drugs like diphenoxylate with atropine have not been thoroughly studied in IBS and may be used less frequently because of these undesirable effects which include dry mouth, sedation, urinary retention and constipation especially due to their anticholinergic property (Wall *et al*., 2014). Codeine phosphate poses a high risk of misuse particularly when overused and in this regard, it is better to avoid in IBS (Hammerle and Surawicz, 2008).

Antispasmodics: Antispasmodic medications had been used for several years in the relief of Irritable Bowel Syndrome (IBS), which is a disease that involves pain in abdomen, abdominal discomfort and alteration of bowel movements. These medications are mainly effective in relieving visceral hypersensitivity and intestinal motility which are the fundamental factors in the pathogenesis of IBS. Antispasmodics also act on

the calcium channels that are important in the contraction of smooth muscles. Alverinecitrate is among the major antispasmodic agents used in treatment of IBS and the muscle relaxant. Alverine citrate reduces calcium mediated smooth muscle contraction and is effective and safe for relieving abdominal pain and discomfort when used with simethicone. Mebeverine is a musculotropic agent that interrupts peristalsis of the intestines and while the earlier reports of the studies were favorable results, recent controlled studies have found no added value in terms of effectiveness to that of a placebo. Otilonium bromide is a L-type calcium channel antagonist and the drug possess antimuscarinic and NK2 receptor antagonism, providing benefits in both pain reduction and improvement of stool form. Similarly, Pinaverium bromide is another L-type that improves stool consistency and treat other motility problem. Phloroglucinol has been found to be effective in decreasing abdominal pain by acting on voltage-gated calcium channels (Annaházi *et al*., 2014).

Antibiotics: Evidence shows that gut microbiota are intimately involved in IBS symptoms, particularly small intestinal bacterial overgrowth (SIBO). This has resulted in the use of antibiotics towards the treatment of these symptoms. Studies also indicated that use of neomycin can help in reducing SIBO and alleviate IBS symptoms. However, there is some draw back with neomycin; its clinical resistance rate is high and breath test results does not normalize in 25% of patients. The effects of Rifaximin extend further than the treatment period, and the improvements in bloating and other related symptoms lasts up to 12 weeks after the treatment. Retreatment with rifaximin is beneficial in most cases with little or no bacterial resistance developed. Patients with IBS-C who produce both, hydrogen and methane need to take rifaximin and neomycin. Researchers shows that combination leads to enhancing the symptoms. It has been proposed that the use of antibiotics, particularly rifaximin, in the treatment of IBS may be an effective way of managing such a group of patients especially those with IBS with non-constipation. Thus, the researchers in the future could further refine the antibiotic treatments and see whether and how these adjustments can affect bacteria's resistance (Basseri *et al*., 2011).

Antidepressants: Antidepressants like Selective serotonin reuptake inhibitors, tricyclic antidepressants and selective norepinephrine reuptake inhibitors are normally prescribed in moderate and severe IBS because they influence mood, pain perception, and intestinal motility. Side effects that differ depending on the class. Tricyclic antidepressants can cause dose-dependent constipation, dryness of both the mouth and eyes, dizziness, increase in weight and a prolonged QT interval. Selective serotonin-reuptake inhibitors can cause problems such as low sexual drive, restlessness, vomiting, dizziness and loose motions. It has been found that TCAs are probably more effective in IBS-D because this group of drugs may act as anticonstipating agents while SSRIs may be more appropriate for IBS-C because they have prokinetic effect. TCAs are also helpful in treating IBS patient with sleeplessness or weight loss while SSRIs is especially helpful in intensive anxiety patient (Chey *et al*., 2015). Tricyclic antidepressants decrease the motility of the gastrointestinal tract while there are indications that the use of selective serotonin-reuptake inhibitors increases the motility of the gastrointestinal tract, more specifically of the small intestine (Gunn *et al*., 2003). Anxiolytics such as, benzodiapines cannot be prescribed as first line therapy for patient of IBS due to side effects and potential dependence (Hadley and Gaarder, 2005).

Laxatives: Laxatives as a treatment of constipation have been employed frequently in the IBS-C patients. Four classes of laxatives are available -- the osmotic laxatives, the stimulant laxatives, the bulking agents and the surfactant laxatives. Laxatives such as corn fibre, wheat bran, ispaghula/psyllium husk and calcium polycarbophil are often used for increasing the oro-anal and colonic transit time in IBS with constipation (Tack *et al*., 2006). Milk of magnesia,

lactulose and sorbitol are the examples of osmotic laxatives. These have at times been advised as initial treatments for patients of IBS with constipation who do not respond to the fibre supplements and dietary fibre. Osmotic laxatives are known to cause abdominal discomfort, increased diarrhoea and, in clinical practice seems to be poorly tolerated. PEG solutions might be easily tolerated in IBS with constipation (IBS-C) due to less bloating is produced. Stimulant laxaives contains phenolphthalein, bisacodyl, danthron, senna and ricinoleic acid. These substances are taken commonly by severe IBS patient. Stimulant laxatives may cause abdominal pain and, while the theoretical risk of colonic myenteric plexus damage is associated with over-the-counter stimulant laxatives, this does not seem to happen in real life (Talley, 2003).

Novel therapeutic strategies for IBS

Chloride channel: Lubiprostone which is a chloride channel activator of local action causes increased secretion of fluids in the intestine (Halland and Talley, 2013). Lubiprostone targets type-2 chloride channels and is present on the apical surface of gastrointestinal epithelial cells and enhances the secretion of electrolyte-rich fluid in the small intestine, which helps boost motility (Hammerle and Surawicz, 2008). High rates of nausea (not more than 25%) have been a problem (Halland and Talley, 2013). Lubiprostone drug was approved by FDA for chronic constipation treatment in year 2006. Sucampo Pharmaceuticals requested FDA approval for the use of lubiprostone in the treatment of IBS-C in a supplemental New Drug Application submitted in September 2007 (Hammerle and Surawicz, 2008).

Guanyl Cyclase-C Receptor Agonist: Plecanatide and Linaclotide are the medications which act as agonists for the guanylate cyclase-C (GC-C) receptor agonist which is found in the gastrointestinal tract, and promotes secretion of chloride and efflux of cyclic guanosine monophosphate (cGMP). The outcomes include both antinciceptive effect intracellular chloride secretion which reduce the pain (Lacy *et al*., 2015). Linaclotide binds to GC-C receptors in linings of intestines and cause secretion of chlorides and bicarbonates into the lumen of the intestines. This results in improved intestinal movement, which might help with the symptoms of IBS (Adeyemo and Chang, 2008). GC–C is a membrane-bound receptor that has important functions concerning the controlling of fluid and electrolyte balance in intestine. In homeostatic physiology, it is stimulated by the internal hormones such as uroguanylin, guanylin and while bacteria toxins activate GC-C as part of the disease process leading to diarrhoea. The guanylin peptides are released into the intestinal lumen by the epithelial cells in an autocrine or paracrine manner thereby promoting the production of cGMP which activates the three major targets of cGMP: cGMP dependent phosphodiesterases, protein kinases, and cyclic nucleotide-gated channels. This results in the increased concentration of bicarbonate, chloride (Cl), and fluid into the intestinal lumen through the cystic fibrosis transmembrane conductance regulator (CFTR) Chloride channel. Movement of cGMP from unrotated epithelia into the basolateral extracellular matrix in the murine colon influences signaling in the sensory as in the case of uroguanylin inhibitory effect on colorectal afferents. This raises another idea of possible involvement of GC-C activation in pain regulation (Longstreth and Drossman, 2002).

5-HT4 agonists: Effect of 5-HT4 agonists is explained by promoting the secretion and motility due to release of acetylcholine from activating motor neurons and connecting neurons (Simrén and Tack, 2018). These drugs have the effect on electrolyte secretion, smooth muscle tone and peristaltic reflex through the initiation of 5-HT4 receptors. As a 5-HT4 agonist, Tegaserod increases the intestinal secretion of chloride and water, thereby decreasing the pain inducing response to rectal distension. Tegaserod was the first medicine approved for female with IBS with constipation (IBS-C) and in male and female younger than 65 for the treatment of chronic idiopathic constipation. Nevertheless, it was

withdrawn from most of the markets, because of the safety of cardiovascular adverse event concerns (Hammerle and Surawicz, 2008). Prucalopride is another 5-HT4 agonist, to which alterations in the chemical structure have provided more selective and safer pharmacological profile and is currently used for the treatment of chronic constipation (Simrén and Tack, 2018). Prucalopride is relatively selective for 5-HT4 agonist, but it was claimed, that it can cause intestinal carcinogenicity when tested on animals (Hammerle and Surawicz, 2008). 5-HT4 agonists not only enhance the gastrointestinal motility but also facilitate to reduce the major symptoms of IBS including bloating, abdominal discomfort, and abdominal pain (Simrén and Tack, 2018).

5-HT3 Agonists: The action of a 5-HT3 receptor agonist pumosetrag (MKC-733) on gastric and small bowel motility was studied in healthy volunteers. The agent at 4 mg dose was observed to be delayed gastric emptying, caused relaxation of proximal stomach, enhanced activity of fasting antroduodenal migrating motor complex, and improved small intestine transit. The effect of pumosetrag on colonic transit was not examined, however, 15% of the subjects reported that the agent made their stools softer or caused diarrhoea implying that pumosetrag has potential for use in the treatment of constipation. Although a quarter of these subjects developed nausea, half of the subjects had flushing and itching, and the systemic effect of serotonin may be the reason behind this. In animal models, 5-HT3 agonists given produced delay in heart rate and reduction in blood pressure. Thus, more human investigations for evaluating the possible involvement of 5-HT3 agonists in IBS or other digestive disorders are necessary. On this basis it can be said that the clinical application may be influenced by such side effects as gastrointestinal and systemic (Andresen and Camilleri, 2006).

5-HT3 Antagonists: 5-HT3 antagonists include inhibition of gastrointestinal transit, reduction of secretion and enhancement of colonic compliance on distension. Improvement of abdominal pain may be associated to central effects on the 5-HT3 receptor site in the brain, where serotonin is also used as a neurotransmitter (Andresen and Camilleri, 2006). The first drug for the treatment of IBS-D to be approved by the FDA was alosetron. It acts as a 5-HT3 antagonist that slows down transit time of colon, enhances absorption of fluid and reduces visceral hypersensitivity and these effects are attributed to compromised blood flow to certain areas of the brain involved with emotions. In patients with IBS-D, alosetron resulted in a relief of abdominal pain and a decrease in the frequency of stool as well as an enhancement of stool consistency. After being taken off the market in 2002 due to issues with constipation and ischemic colitis, alosetron was reintroduced with limitations, such as the implementation of the Risk Management Program (RMP) (Hammerle and Surawicz, 2008; Nee *et al*., 2015). Cilansetron is another 5HT-3 which is also used in development of both male and female IBS-D, with onset of efficacy that is similar to alosetron. However, in clinical trials, cilansetron was linked with constipation and few cases of ischemic colitis and for this the US-FDA rejected its approval in April 2005 but demanded more clinical trials. As for the relation between 5-HT3 antagonists and ischemic colitis more clarification is required, and studies must be done on risk factors (Andresen and Camilleri, 2006).

5-HT$_4$ antagonists: 5-HT4 antagonists are involved in the regulation of secretion of excitatory neurotransmitters incorporating substance-P, acetylcholine and calcitonin gene-related peptide that control peristalsis. Some of these receptors have been postulated to be targeted selectively for the treatment of IBS-D in order to alleviate the related symptoms. This mechanism may affect colonic transit time and enhance the rectal sensitivity which possibly is beneficial for the G.I. symptoms in IBS-D patients. More studies on 5-HT4 antagonists are needed so as to establish the effectiveness of these compounds and their medical use (Hammerle andSurawicz, 2008).

Peppermint Oil: When recommending peppermint

oil for IBS one has to consider the source of the products and the quality of different batches as these products are over-the-counter and are not managed by the FDA. Nonetheless, peppermint oil has been thoroughly investigated, and the evidence has demonstrated that it is effective and have minimal side effects for the management of IBS. The starting dose for peppermint oil can be taken at 550 mg once a daytime or 187 mg thrice at different times of the day. The side effects reported with the use of peppermint oil in the trials were only comparable to the placebo, which included two incidences of heartburn, one that was because of a patient chewing on the substance. Besides heartburn, the side effects that were reported among the general users of peppermint oil are nausea and vomiting. Some products containing peppermint oil in enteric coated capsules may reduce or eliminate heart burn. To remind the patient to buy and consume the prescribed product as well as its appropriate dose, the clinician has to write a prescription to the pharmacist as well as the patient (Trinkley and Nahata, 2014).

Eluxadoline: Eluxadoline – is a drug acting as a μ-receptor agonist and κ-receptor agonist as well as a δ-opioid receptor antagonist. The action on the μ-receptor reduces the pain in abdomen and also reduces the propulsion of gastrointestinal tract. By acting on the δ-receptor, the drug's μ agonist effect avoids the over-inhibition of gastrointestinal motility and offers pain relief without causing tolerance. In animal studies of gastrointestinal dysmotility disorders, eluxadoline helps regulate stool outputs without fully inhibiting the gastrointestinal transit, which differs from loperamide, a pure μ-opioid receptor agonist. The adverse effects occur in patients of IBS administered eluxadoline include nausea, abdominal pain and vomiting. Constipation was usually seen as a minimal adverse effect with the 100 mg dosage. The only well-known serious risk associated with this drug is the risk of spasm in the sphincter of Oddi leading to pancreatitis. Currently, the FDA advises that eluxadoline is contraindicated for patients with a bile duct obstruction history, pancreatitis, severe liver dysfunction, or a history of chronic constipation and who drink more than 3 alcoholic beverages a day (Wadhwa *et al*., 2015).

Tenapanor: At present, Tenapanor (RDX-5791) is in the phase III trials for the treatment of IBS with Conspitation (IBS-C) and chronic idiopathic constipation(CIC). It selectively blocks the NHE3 transporter that are well involved in controlling sodium level in the body. *In vitro* studies indicate specificity for NHE3 compared to analogous transporters including NHE1, NHE2, and NaP2b. Clinical trials demonstrate a decrease in the median time to the first post-treatment bowel movement, an improvement in stool consistency as determined by the Bristol Stool Form Scale (BSFS), and an increase in average stool weight. Pharmacodynamic response was significantly higher with twice-daily dosing. Tenapanor has been proved to be effective to alleviate symptoms of IBS-C patients such as abdominal pain, bloating, stool consistency, bowel frequency and quality of life. The most commonly reported side effect was diarrhea, although the drug's poor bioavailability helps to maintain an overall good safety profile (Nusrat and Miner, 2015).

ROSE-010: The hormone analog ROSE-010 of the glucagon-like peptide-1 (GLP-1) hormone was suggested to alleviate the pain component of IBS by focusing on abnormality of the motor activity in gut. GLP-1 decreases the motility of the small intestine in both IBS patients as well as healthy individuals. Stool consistency, stool frequency, small bowel or colonic transit, and stomach volumes were not significantly impacted by ROSE-010. Some of these doses increases colonic transit, The clinical relevance of such changes in colonic transit remains equally unclear. Some of the side effect associated with the drugs were vomiting and nausea (Wadhwa *et al*., 2015).

AST 120: AST-120 is a spherical carbon adsorbent that has been initially prescribed to slow the advancement of renal failure and is presently under consideration to treat other types of IBS that are not constipation predominant. Patients

with non-constipation IBS have showed a notable improvement in bloating and stomach discomfort reduction. AST-120 stabilizes the contents of feces, with moderate efficiency, and does not aggravate side effects in comparison with placebo (Trinkley and Nahata, 2014)/

Ibodutant: Ibodutant is a neurokinin-2 receptor antagonist which has been used in treating IBS-D,(Trinkley andNahata, 2014). It functions by focusing on tachykinins, which stimulate smooth muscle and inhibit nitrergic neurons to cause smooth muscle contraction in the colon (Wadhwa *et al*., 2015). A number of clinical trials have proven that ibodutant results in a better improvement of abdominal pain, alleviates satisfactory overall symptom, and enhances IBS-D patient's quality of life as compared to the placebo (Trinkley and Nahata, 2014). The most effective dose among those examined was 10 mg once day and females reported better results than males (Trinkley and Nahata, 2014).

Conclusion

Irritable Bowel Syndrome (IBS) is a complex, multifactorial disorder affecting gastrointestinal function and significantly impacting patients' quality of life. Recent advances in understanding IBS have emphasized the role of diet, stress, microbiota, and visceral hypersensitivity in its pathophysiology. These insights have paved the way for innovative therapeutic approaches, particularly in the realm of pharmaceuticals and dietary management. Novel therapeutic strategies, such as chloride channel activators (e.g., lubiprostone), guanylate cyclase-C agonists (e.g., linaclotide), 5-HT receptor modulatorsetc, show promise in alleviating symptoms, particularly in specific IBS subtypes. Probiotics and dietary fibers also continue to play a vital role in managing symptoms, especially for those with IBS-C. Meanwhile, non-pharmacological approaches like cognitive behavioral therapy (CBT) and stress management offer additional avenues for relief, emphasizing the importance of a holistic, personalized approach in managing IBS. Moving forward, ongoing research will likely further refine these treatments, offering improved quality of life for IBS patients.

Ethical Statement

This is a review article thus an ethical statement is not needed.

Author Contributions

Each author equally shared in the study's planning, writing, editing, designing the research, conducting thorough analysis, drafting the manuscript, and refining its content. All authors have read and agreed to the published version of the manuscript.

Conflict of Interest

The authors declare no conflicts of interest.

References

Adeyemo MA and Chang L. (2008) New treatments for irritable bowel syndrome in women. Womens Health (Lond) 4(6): 605-622.

Algera J, Colomier E and Simrén M. (2019) The dietary management of patients with irritable bowel syndrome: A narrative review of the existing and emerging evidence. Nutrients 11(9): 2162.

Andresen V and Camilleri M. (2006) Irritable bowel syndrome. Drugs 66: 1073-1088.

Annaházi A, Róka R, Rosztóczy A and Wittmann T. (2014) Role of antispasmodics in the treatment of irritable bowel syndrome. World J Gastroenterol. 20(20): 6031-6043.

Barbara G, De Giorgio R, Stanghellini V, Cremon C, Salvioli B and Corinaldesi R. (2004) New pathophysiological mechanisms in irritable bowel syndrome. Alimentary Pharmacol Therapeutics 20(s2): 1-9

Barbara G, Dolci M, Cremon C, Barbaro MR, Bellacosa L, Fucili A and Stanghellini V. (2013) Understanding the pathophysiology of IBS. EMJ Gastroenterol. 1: 40-46.

Basseri RJ, Weitsman S, Barlow GM and Pimentel M. (2011) Antibiotics for the treatment of irritable bowel syndrome. Gastroenterol Hepatol (NY) 7(7): 455-493.

Black CJ and Ford AC. (2020) Best management of irritable bowel syndrome. Frontline Gastroenterol. 12(4): 303-315.

Cash BD and Chey WD. (2004) Irritable bowel syndrome - An evidence-based approach to diagnosis.

Alimentary Pharmacol Therapeutics 19(12): 1235-1245.

Chey WD, Kurlander J and Eswaran S. (2015a) Irritable bowel syndrome: A clinical review. JAMA. 313(9): 949-958.

Chong PP, Chin VK, Looi CY, Wong WF, Madhavan P and Yong VC. (2019) The microbiome and irritable bowel syndrome - A review on the pathophysiology, current research and future therapy. Front Microbiol. 10: 1136.

Coutts A. (2019) Nursing management of irritable bowel syndrome. Nurs Stand. 34(5): 76-81.

Ford AC, Moayyedi P, Lacy BE, Lembo AJ, Saito YA, Schiller LR, Soffer EE, Spiegel BM, Quigley EM; and Task Force on the Management of Functional Bowel Disorders (2014) American college of gastroenterology monograph on the management of irritable bowel syndrome and chronic idiopathic constipation. Am J Gastroenterol. 109 Suppl 1: S2-26.

Gasbarrini A, Lauritano EC, Garcovich M, Sparano L and Gasbarrini G. (2008) New insights into the pathophysiology of IBS: intestinal microflora, gas production and gut motility. Eur Rev Med Pharmacol Sci. 12 Suppl 1: 111-117.

Goldstein RS and Cash BD. (2021) Making a confident diagnosis of irritable bowel syndrome. Gastroenterol Clin North Am. 50(3): 547-563.

Grad S and Dumitrascu DL. (2020) Irritable bowel syndrome subtypes: New names for old medical conditions. Dig Dis. 38(2): 122-127.

Gunn MC, Cavin AA and Mansfield JC. (2003) Management of irritable bowel syndrome. Postgrad Med J. 79(929): 154-158.

Hadjivasilis A, Tsioutis C, Michalinos A, Ntourakis D, Christodoulou DK and Agouridis AP. (2019) New insights into irritable bowel syndrome: from pathophysiology to treatment. Ann Gastroenterol. 32(6): 554-564.

Hadley SK and Gaarder SM. (2005) Treatment of irritable bowel syndrome. Am Fam Physician. 72(12): 2501-2506.

Halland M and Talley NJ. (2013) New treatments for IBS. Nat Rev Gastroenterol Hepatol. 10(1): 13-23.

Hammerle CW and Surawicz CM. (2008) Updates on treatment of irritable bowel syndrome. World J Gastroenterol. 14(17): 2639-2649.

Hiatt RB and Katz L. (1962) Mast cells in inflammatory conditions of the gastrointestinal tract. Am J Gastroenterol. 37: 541-545.

Karantanos T, Markoutsaki T, Gazouli M, Anagnou NP and Karamanolis DG. (2010) Current insights in to the pathophysiology of Irritable Bowel Syndrome. Gut Pathogens 2: 3.

Khan S and Chang L. (2010) Diagnosis and management of IBS. Nat Rev Gastroenterol Hepatol. 7(10): 565-581.

Kirsch R and Riddell RH. (2006) Histopathological alterations in irritable bowel syndrome. Mod Pathol. 19(12): 1638-1645. Erratum in: Mod Pathol. 2007 20(2): 278.

Kurien M, Evans KE, Leeds JS, Hopper AD, Harris A and Sanders DS. (2011) Bile acid malabsorption: an under-investigated differential diagnosis in patients presenting with diarrhea predominant irritable bowel syndrome type symptoms. Scand J Gastroenterol. 46(7-8): 818-822.

Lackner JM, Jaccard J, Krasner SS, Katz LA, Gudleski GD and Blanchard EB. (2007) How does cognitive behavior therapy for irritable bowel syndrome work? A mediational analysis of a randomized clinical trial. Gastroenterology 133(2): 433-444.

Lacy BE, Chey WD and Lembo AJ. (2015) New and emerging treatment options for Irritable Bowel Syndrome. Gastroenterol Hepatol. (NY) 11(4 Suppl 2): 1-19.

Lewis SJ and Heaton KW. (1997) Stool form scale as a useful guide to intestinal transit time. Scand J Gastroenterol. 32(9): 920-924.

Longstreth GF and Drossman DA. (2002) New developments in the diagnosis and treatment of irritable bowel syndrome. Curr Gastroenterol Rep. 4: 427-434.

Moayyedi P, Mearin F, Azpiroz F, Andresen V, Barbara G, Corsetti M, Emmanuel A, Hungin APS, Layer P, Stanghellini V, Whorwell P, Zerbib F and Tack J. (2017) Irritable bowel syndrome diagnosis and management: A simplified algorithm for clinical practice. United European Gastroenterol J. 5(6): 773-788.

Nee J, Zakari M and Lembo AJ. (2015) Novel therapies in IBS-D treatment. Curr Treat Options Gastroenterol. 13(4): 432-440.

Nusrat S and Miner PB. (2015) New pharmacological treatment options for irritable bowel syndrome with constipation. Expert Opin Emerg Drugs 20(4): 625–636.

Pietrzak A, Skrzydło-Radomańska B, Mulak A, Lipiński M, Małecka-Panas E, Reguła J and Rydzewska G. (2018) Guidelines on the management of irritable bowel syndrome: In memory of Professor Witold Bartnik. Prz Gastroenterol. 13(4): 259-288.

Qin HY, Cheng CW, Tang XD and Bian ZX. (2014) Impact

of psychological stress on irritable bowel syndrome. World J Gastroenterol. 20(39): 14126-14131.

Quigley EM, Fried M, Gwee KA, Khalif I, Hungin AP, Lindberg G, Abbas Z, Fernandez LB, Bhatia SJ, Schmulson M, Olano C and LeMair A. (2016) World Gastroenterology Organisation global guidelines irritable bowel syndrome: a global perspective update September 2015. J Clin Gastroenterol. 50(9): 704-713.

Raskov H, Burcharth J, Pommergaard HC and Rosenberg J. (2016) Irritable bowel syndrome, the microbiota and the gut-brain axis. Gut Microbes. 7(5): 365-383.

Scalera A and Loguercio C. (2012) Focus on irritable bowel syndrome. Eur Rev Med Pharmacol Sci. 16(9): 1155-1171.

Simrén M and Tack J. (2018) New treatments and therapeutic targets for IBS and other functional bowel disorders. Nat Rev Gastroenterol Hepatol. 15(10): 589-605.

Soares RL. (2014) Irritable bowel syndrome: a clinical review. World J Gastroenterol. 20(34): 12144-12160.

Spiller RC, Jenkins D, Thornley JP, Hebden JM, Wright T, Skinner M and Neal KR. (2000) Increased rectal mucosal enteroendocrine cells, T lymphocytes, and increased gut permeability following acute Campylobacter enteritis and in post-dysenteric irritable bowel syndrome. Gut 47(6): 804-811.

Suares NC and Ford AC. (2011) Prevalence of, and risk factors for, chronic idiopathic constipation in the community: systematic review and meta-analysis. Am J Gastroenterol. 106(9): 1582-1591.

Tack J, Fried M, Houghton LA, Spicak J and Fisher G. (2006) Systematic review: the efficacy of treatments for irritable bowel syndrome--a European perspective. Aliment Pharmacol Ther. 24(2): 183-205.

Talley NJ. (2003) Evaluation of drug treatment in irritable bowel syndrome. British J Clin Pharmacol. 56(4): 362-369.

Tolliver BA, Herrera JL and DiPalma JA. (1994) Evaluation of patients who meet clinical criteria for irritable bowel syndrome. Am J Gastroenterol. 89(2): 176-178.

Trinkley KE and Nahata MC. (2014) Medication management of irritable bowel syndrome. Digestion 89(4): 253-267.

Viera AJ, Hoag S and Shaughnessy J. (2002) Management of irritable bowel syndrome. Am Fam Physician. 66(10): 1867-1874.

Wadhwa, A, Camilleri M and Grover M. (2015) New and investigational agents for irritable bowel syndrome. Curr Gastroenterol Rep. 17: 46.

Wall GC, Bryant GA, Bottenberg MM, Maki ED and Miesner AR. (2014) Irritable bowel syndrome: a concise review of current treatment concepts. World J Gastroenterol. 20(27): 8796-806.

Weaver KR, Melkus GD and Henderson WA. (2017) Irritable Bowel Syndrome. Am J Nurs. 117(6): 48-55.