TREATMENT OF IRRITABLE BOWEL SYNDROME: A REVIEW

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ABSTRACT

Irritable bowel syndrome (IBS) is a gastrointestinal disease which is also called as spastic colon, mucous colitis is characterized by some non-specific symptoms, such as altered bowel habits and abdominal pain, stomach bloating, chronic diarrhea or constipation or alternating between the two. The therapy is based on the healing of symptoms using various pharmaceutical and non-pharmaceutical agents. The objective of treatment is relief from symptom and improved quality of life. The approach for the treatment of IBS is based on the predominant symptoms of the patient. Classical as well as alternative treatment both appear to be effective for the patients. Classical treatments basically consist of anti-diarrheal, antidepressants, antispasmodic, bulking agents, osmotic laxatives, etc. Still, herbal or alternative treatment always seems to be the same beneficiary for the patients due to their negligible adverse effect.

Keywords: Irritable bowel syndrome, Symptoms, Treatment, Alternative treatment, Alter medicine.

INTRODUCTION

Irritable bowel syndrome (IBS) is referred to as a gastrointestinal (GI) syndrome, which is differentiated by altered bowel habits and chronic abdominal pain, and no organic cause is identified for this condition [1,2]. IBS is a common disease in the general population and its prevalence varies from country to country and the criteria used for the diagnosis of IBS [3]. It is also described on the basis of symptoms reported by the patients with recurrent abdominal pain or discomfort at least 3 days a month in the previous 3 months, interconnected with two or more of the following: Improvement with defecation, onset associated with a change in frequency of stool, and onset associated with a change in the appearance of stool [4,5]. IBS is moreover classified into diarrhea-predominant IBS (IBS-D), constipation-predominant IBS (IBS-C), and mixed symptom IBS (IBS-M) [6,7].

An essential approach expresses that the walls of the digestive organs are fixed with layers of muscle that contract and relax as they move food from one's stomach through the intestinal tract to the rectum. However, people with IBS appear to have an impedance in the communication between the brain, and the musculature of the gut resulting in too little or a lot of mobility. Besides, triggering of IBS like foods (highly fatty and spicy foods) stress, and beverages (alcohol and caffeine) have a tendency to worsen the symptoms of IBS [8,9].

Pathogenesis

The underlying causes of IBS remain to be adequately identified.

Serotonin dysregulation

Serotonin acting, especially through the 5-hydroxytryptamine Type 3 (5-HT₃) and 5-HT₄ (5-HT) receptors play a critical role in the control of GI motility, sensation, and secretion [10,11]. 5-HT₃ receptors are mainly responsible for the regulation of GI motor function through its action on nerve receptors within the enteric nervous system and are involved in the modulation of the visceral sensory function [12]. Moreover, perceptions have demonstrated that plasma 5-HT concentrations are reduced in IBS patients with constipation but raised in those with diarrhea [13].

The role of bacterial flora in IBS

Changes in the amount and nature of the microscopic organisms present can pass selective effects on sensory-motor dysfunctions which can be affected by bile acid malabsorption, mucosal irritation and inflammation, increased food fermentation, and gas generation. Increased fecal numbers of lactobacilli, coliform, and bifidobacteria have been reported in patients affected by IBS [14,15]. Probiotics have the potential to lessen intestinal permeability and the generation of pro-inflammatory cytokines that are hoisted in patients with an assortment of hypersensitive disorders [16].

Visceral hypersensitivity

Visceral hypersensitivity is viewed as a key component in the pathogenesis of pain perception in patients with IBS. Hypersensitivity to swell distension of the rectum was at first identified in 95% of IBS patients, but subsequently shown to be present in only about half of patients, especially those with IBS-D [17].

TREATMENT

Medication treatment might be started when IBS symptoms begin to reduce the patient’s personal satisfaction. Traditional pharmacological treatment for IBS depends on the event of symptoms. The symptoms are, however, named per the types of IBS.

IBS-C

Fibers

IBS sufferers were recommended to expand dietary fiber supplements. There are mostly two kinds of fiber, that is soluble (e.g. bulking agents - psyllium) and insoluble (e.g. wheat bran). An insoluble fiber causes the gathering of gas, bloating, distension, and abdominal pain. Psyllium hydrophilic mucilloid (ispaghula husk) might be given in a conditional recommendation. A single study reported improvement with calcium polycarbophil. It is one of the helpful treatment for IBS-C treatment which stimulates GI motility and relaxes stool consistency [18,19]. Day by day administration of insoluble dietary fiber has a consequent improvement in the severity of constipation. This dietary filament also produced improvements in the patients’ motor scoring likely because of better retention of L-dopa, which was clear by substantially higher total plasma L-dopa levels [20].
**Prokinetics**
Prokinetic is an agent which improves the GI motility by expanding the recurrence of contractions in the small intestine or making them stronger, but without disrupting their rhythm. Examples: VSL#3, LP299W.

**Anticholinergics**
Essentially, it works by decreasing visceral sensation and colonic transit by decreasing the secretion from the intestinal gland. Example: Zamifenacin.

**Dopamine antagonists**
Most broadly utilized prokinetic agent was metoclopramide (dopamine antagonist) with central and peripheral effects. Iopidine hydrochloride is a prokinetic drug that activates the GI motility through the synergism of its dopamine D2 receptor antagonistic action and its acetylcholine esterase inhibitory activity [21]. Domperidone, a dopamine antagonist that does not cross the blood-brain barrier and work essentially through peripheral dopamine A1 receptors, is available for use.

**Serotonergic agonists**
In the substituted benzamide gathering of prokinetics, cisapride was the prototype [22]. It encourages the release of acetylcholine from myenteric plexus of the neuron through a 5HT1 receptor-mediated effect [23]. In clinical trials, tegaserod (5-HT4 agonist) has been accounted to diminish the general symptoms of IBS patients in comparison to a tested placebo. Recently, it has been demonstrated that tegaserod may increase the risk of ischemic heart disease when compared to placebo; therefore, the use of this medication was restricted in September 2007. Starting in July 2007 tegaserod was only prescribed to ladies under 55-year-old who suffer from IBS with predominant constipation symptoms and no evident indications of cardiovascular disease [24]. Renzapride (mixed serotonin receptor agonist/antagonist). It might be more effective than a single agent and is prescribed for the therapeutic management of the IBS-C, and it encourages motility [25].

**Antibiotics**
There are three general techniques by which the intestinal microflora can be adjusted: Administration of antibiotics or probiotics (i.e. Dietary components that promote the growth and the metabolic activity of beneficial bacteria), or administration of probiotics [26]. Antibiotics are additionally utilized by numerous clinicians to treat IBS symptoms [27]. The enteric flora in IBS patients may differ in correlation with healthy controls which result in increased hydrogen discharge during carbohydrate fermentation. This will further lead to flatulence, constipation and other gastric disturbances. The second line of confirmation to help the utilization of antibiotics in IBS is the connection among IBS and bacterial overgrowth [28,29]. It was recommended to prescribe wide-spectrum antibiotics such as clarktheromycin, ciprofloxacin, amoxicillin, metronidazole, rifaximin, and doxycycline for 10 days [30].

**Laxatives**
The most critical intestinal medicines are divided into four groups: Fecal softeners (e.g. liquid paraffin), stimulant laxatives (e.g. bisacodyl), osmotic laxatives (e.g. methyl cellulose), and bulk-forming laxatives (ispaghula husk) [31].

**Diarrhea predominant IBS**
IBS-D shows quicker intestinal transit when compared with healthy subjects and therefore, agents which delay intestinal transit may be useful in reducing symptoms.

**Antispasmodics**
This is the agents which relax smooth muscle by means of calcium channel antagonist, or anticholinergic mechanisms have been ordinarily used for the treatment of IBS. Medication such as alverine, dicyclomine, hyoscymamine, and scopolamine has been used for their effects on GI motility in endeavors to decrease abdominal pain associated with IBS. They are also used in combination with agents such as acetaminophen, simethicone, and benzodiazepines in attempts to enhance GI discomfort [32,33].

**Antidiarrheal drugs**
A synthetic phenylpiperidine subsidiary loperamide is first approved by the USFDA for the treatment of diarrhea in 1976. By restraining both intestinal secretion and peristalsis, loperamide slows down intestinal transit and allows for increased fluid reabsorption, hence improving symptoms of diarrhea. Diphenoxylate and atropine in the blend are frequently used to treat symptoms of acute and chronic diarrhea [34,35].

**5-HT4 antagonist**
Alosetron is a powerful and specific 5-HT4 receptor antagonist. It acts by backing off colonic transit and increase small intestinal fluid absorption and enhances visceral pain [36,37]. For ladies with IBS-D, alosetron has been appearing to be strong in several randomized, placebo-controlled studies [38]. Constipation is the most common adverse effect associated with its utilization [27].

**Antidepressants**
At a low amount, antidepressant has been appeared to diminish the pain. Tricyclic antidepressants will encourage the arrival of endogenous endorphin and block norepinephrine reuptake, which prompts for the enhancement of descending inhibitory pathway blockage of the pain neuromodulator serotonin. It might moderate intestinal transit time and helps in the treatment of diarrhea. Two late meta-examination assessed randomized control trials of patients taking low-dosage tricyclic antidepressants, such as clomipramine, desipramine, amitriptyline, doxepin, and trimipramine. These examinations demonstrated that tricyclic antidepressants enhance abdominal pain, and diarrhea [39]. Antidepressants are categorized as selective serotonin reuptake inhibitors, tricyclics and related antidepressants, and monoamine oxidase inhibitors. The medication includes duloxetine, fluoxetine, mirtazapine, reboxetine, tryptophan, and venlafaxine [40–42].

**Newer medicines for both IBS-D and IBS-C**

**Drugs for diarrhea predominant IBS**

**Alosetron**
It works by restraining serotonin signals by antagonizing 5-HT3 receptors that transmit sensory information (painful and non-painful) from the abdomen to the brain and helps to reduce abdominal pain and diarrhea. It has been affirmed for the use in women with severe IBS-D. It has serious side effects so prescribed under a risk management program requires careful checking and education. Alosetron gave a noteworthy decrease in the worldwide symptoms of diarrhea, abdominal pain, and bloating in patients with IBS and diarrhea. 5-HT3 receptors are mostly found in the lumen (enteric nerves) and on higher nerve locations, such as the vomiting center. Obstructing these receptors reduces GI pain, colonic transit, and small intestinal secretion. It is effective in relieving pain and normalizing bowel frequency as well as reducing urgency in diarrhea-predominant, female patients with IBS.

**Rifaximin**
It was approved by United States Food and Drug Administration (USFDA) for treatment of IBS-D in adults. It works by bringing down microbes in the gut. A course of 10–14 days has been found to redesign IBS
### Table 1: Conventional pharmacological drugs used for the treatment of IBS [54-56]

| Types of IBS                  | Treatment types | Sub types      | Examples                  | Structure |
|-------------------------------|-----------------|----------------|---------------------------|-----------|
| Constipation predominant IBS  | Fibers          | Soluble fibers | Psyllium husk             | -         |
|                               |                 | Insoluble fibers | Wheat bran               | -         |
|                               | Prokinetics     | Anticholinergic | Zamifenacin              | -         |
|                               |                 |                | Metoclopramide           | Domperidone |
|                               |                 |                | Tegaserode               | Renzapride (5-HT4 agonist) |
|                               |                 | Serotonergic agonist |                | Tegaserode |
|                               |                 | Antibiotics    | Metronidazole            | Doxycycline |
|                               | Laxatives       | Osmotic Laxatives | PEG 3350                |           |
|                               |                 | Stimulant laxatives | Lactulose               |           |
|                               | Fecal Softeners |                | Bisacodyl                |           |
|                               | Bulk forming laxatives |            | Docusate sodium         |           |
| Diarrhea Predominant IBS      | Antispasmodics  |                | Dicyclomine              |           |
|                               | Antidiarrheals  |                | Diphenoxylate-atropine combined | Loperamide |
|                               | 5-HT3 antagonist |                | Alosetron                |           |

(Contd...)
symptoms of bloating and diarrhea. Although few patients experience relief of IBS symptoms after taking a course of rifaximin, others require treatment (up to 2 times at the same dosage). It is slightly absorbed in the gut and is generally tolerated well. An underlying little randomized, controlled trial by Pimentel et al. in 87 patients with IBS suggested that a 10 days course of rifaximin 400 mg 3 times daily improved patient global scores of symptoms compared to placebo [29,43].

Eluxadoline
In May 2015, USFDA has approved this medication. It is prescribed for the treatment of IBS-D in adult, men, and women. It likewise diminishes abdominal pain and improves stool consistency. It controls GI motility, secretions, and visceral sensations. It is a mixed mu opioid receptor agonist with a delta-opioid receptor antagonist activity and kappa-opioid agonist activity. An estimated 95% of patients with IBS experience enhanced visceral and sensory responses, which contribute to the symptoms of pain, gas, and intestinal contractions [44].

In patients with IBS-D, there is expanded colonic transit and enhanced peristaltic contractions, most notably after meals. A mixed-opioid medication, such as eluxadoline, provides relief of IBS-D related symptoms with lower rates of side effects, specifically constipation. Pain medications that solely target the mu opioid receptor are known to cause noteworthy constipation and potential for tolerance or dependence. Eluxadoline targets local opioid receptors in the gut, which decreases the chance of additional central nervous system side effects [45,46].

Drugs for IBS-C
Lubiprostone
This medication has been appearing to be viable for treating constipation symptoms. It promotes secretion through chloride channels in the digestive tract, which, in turn, stimulate peristalsis, the coordinated muscle contractions that propel the substance through the GI tract. It was FDA approved in 2006 for the treatment of chronic idiopathic

Table 1: (Continued)

| Types of IBS | Treatment types | Sub types | Examples | Structure |
|-------------|----------------|-----------|----------|-----------|
|             | Antidepressants | -         | Amitriptyline |
|             |                |           | Clomepramine |

IBS: Irritable bowel syndrome

Table 2: Emerging pharmacological drugs used for the treatment of IBS [57-63]

| Class of drug             | Mechanism of action                                    | Examples                          | Structure |
|---------------------------|--------------------------------------------------------|-----------------------------------|-----------|
| α2-adrenergic agonist     | Decrease pain sensation and colonic tone               | Clonidine                         |
| Neurontic agonist         | Increase pain threshold induced by distension          | Fedotozine, Asimadoline          |
| Neurokinin antagonists    | Decrease visceral sensation                             | CJ-11974, MEN-11420, nepadutant   |
| Somatostatin analogs     | Decrease colonic response to distension                 | Octreotide                        |
| Calcium channel blockers | Decrease rectosigmoid response to distension           | Verapamil                         |
| Oxytocin                  | Increase pain threshold induced by colonic distension  |                                    |
| Neutrophils               | Improve constipation                                    | Recombinant human neutrophin-3   |
| Probiotics                | Improve balance of intestinal flora                     | VSL#3, LP299V                     |

IBS: Irritable bowel syndrome
constipation at a dose of 24 μg taken twice per day. This approval was based on the results of two 12-week randomized phase trials that were published in one manuscript in 2009. It is approved for use in women with IBS-C, and in men and women with chronic constipation (without predominant abdominal pain) [47].

**Linaclotide**

It is 14-amino acid synthetic peptide guanylate cyclase-C agonists. It works by increasing the movement of a substance through the GI tract and by blocking pain signals in the intestines. Activation of guanylate cyclase receptors leads to increased secretion of both guanylin and uroguanylin into the intestinal lumen where they act as a second messenger for both electrolyte and fluid release into the large bowel [48-50].

The medicine is prescribed for the treatment of IBS with constipation and chronic idiopathic constipation. I consider, patients taking linaclotide experienced improvement in multiple symptoms, including pain or discomfort, bloating, and bowel function. Preliminary clinical studies were conducted in the mid-2000s and found the medicine to have significant effects on ascending colonic transit time and clinical symptoms related to stooling, diarrhea, abdominal pain, flatulence, and abdominal distension are the most common adverse effects of this drug [51-53].

**TREATMENT OF MIXED SYMPTOM IBS**

The symptoms for mixed symptom IBS involve an alternating cycle of diarrhea and constipation. Treatment of alternating type IBS or what we called as mixed symptom IBS can be challenging. Henceforth, treatment regimen is classified into a combination of both IBS-D and IBS-C. This is because of the fact that bowel symptoms move to and fro from diarrhea to constipation and back again. It is a common concern that steps taken to address one symptom will result in bringing on the unwanted effects of the other. However, we can take a portion of the measures to keep up the side effects.

**Alternative treatment of IBS**

**Peppermint oil**

Peppermint oil is extracted from *Mentha piperita*. Lamiaceae by the steam distillation process are among the oldest remedies for the treatment of GI issues. The major constituent of peppermint oil is menthol, which has an antispasmodic agent that blocks L-type calcium channels, resulting in GI smooth muscle relaxation [64-66]. It applies a spasmolytic effect on the smooth muscles in the digestive tract and believed to improve IBS symptoms. Gastroesophageal reflux is the most common adverse effect associated with oral peppermint oil. Peppermint oil is a standout among the most commonly used over-the-counter remedies [67-69].

**Turmeric extract**

It is obtained from the dried rhizome of *Curcuma longa*, Zingiberaceae. The extract of rhizomes tends to show maximum activity for the symptoms of IBS. 8-week treatment of IBS patients with *C. longa* extract tablet tends to decrease IBS prevalence and abdominal pain/discomfort [70]. The inhibitory effects of the extract of turmeric (curcumin) are mediated fundamentally through a calcium channel blockade in hyperactive states of the gut and airways [71].

**Ginger rhizomes**

It is the oleoresin obtained from the fresh rhizome of *Zingiber officinale*, Zingiberaceae. Ginger dosing is standardized according to gingerol content which is accepted to have antiemetic, pain relieving, sedative, antibacterial, and other physiological effects [72]. It has an aromatic odor and tangy and pungent taste [73].

**Chamomile drops**

It consists of dried flowering tops of chamomile *Matricaria chamomilla*, Asteraceae. The flowers of chamomile contain 1-2% volatile oils including alpha-bisabolol, alpha-bisabolol oxides A and B, and matricin (usually converted to chamazulene and other flavonoids. Which possess anti-inflammatory and anti-angiogenic properties) [74-76]. Chamomile is especially helpful in eliminating gas, soothing the stomach, and relaxing the muscles that move food through the intestines. Chamomile is used traditionally for digestive disorders, “spasm” or colic, upset stomach, flatulence (gas), ulcers, and GI irritation as well as disorders of the nervous system and dysmenorrhea [77,78].

**CONCLUSION**

The IBS is the most common GI disorder seen in primary care. The pathophysiology of the IBS is complex and unclear. Both central and
The effect of the 5-HT3 receptor antagonist, functional bowel disorders. Gastroenterology International survey of patients with IBS: Symptom features

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