A REVIEW ON RECENT APPROACHES IN TREATMENT OF IRRITABLE BOWEL SYNDROME

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ABSTRACT

Irritable bowel syndrome (IBS) is the most prevalent functional gastrointestinal disorder noted in the general population worldwide characterized by abdominal pain associated with abnormal bowel movement without any clinically identifiable structural or biochemical abnormality. The pathophysiology of IBS is considered to be multifactorial, involving disturbances of the brain-gut-axis: IBS has been associated with abnormal gastrointestinal motor functions, visceral hypersensitivity, psychosocial factors, autonomic dysfunction and mucosal inflammation. Traditional IBS therapy is mainly symptom oriented and often unsatisfactory. Hence, there is a need for new treatment strategies. Increasing knowledge of brain-gut physiology, mechanisms, and neurotransmitters and receptors involved in gastrointestinal motor and sensory function have led to the development of several new therapeutic approaches. Recent studies have suggested that probiotics may be useful in the treatment of IBS. The effects of probiotics on alterations in gut bacteria appear to play a part. This article provides a systematic overview of recently approved or novel medications that show promise for the treatment of IBS.

Keywords: Irritable bowel syndrome, gut motility, visceral hypersensitivity, brain-gut axis, alternating diarrhea and constipation.

INTRODUCTION

Irritable bowel syndrome (IBS) is the most common reason for referral to gastroenterology clinics.[1] The disease is characterized by abdominal pain, diarrhea, constipation or a combination of both diarrhea and constipation, mucus discharge along with stools and changes in the form (appearance) of stools. The main cause of disease is not entirely apparent as various factors play key roles in its etiology. IBS is a disorder that is not confirmed by a specific test. Instead diagnosis is based on specific symptoms termed the Rome criteria. Ruling out other conditions that cause similar signs and
symptoms is essential for an accurate diagnosis. [2,3] It occurs in approximately 15% of adults in Western countries. [4, 5] It was first described by Osler in 1892 [6] as a disorder characterized by the passage of tubular casts of the colon, consisting of mucus, cell debris, and “pultaceous stools.” Ambiguities in defining the syndrome, lack of understanding of its pathophysiology, and slow accumulation of evidence on the benefits of treatment modalities have made IBS notoriously difficult to diagnose and treat. [7]

Epidemiology

Irritable bowel syndrome is diagnosed most frequently in young adults who have recurrent or chronic gastrointestinal symptoms, usually consisting of abdominal pain and altered bowel habits. [8] Classic features of IBS include triggering of symptoms caused by stress or diet, relief of pain with defecation, and irregularity of bowel movements. [9] In the United States annually, IBS accounts for 3.5 million physician visits, predominantly by adult female patients. [10] It is the most common cause for referral to gastroenterologists, constituting 20% to 50% of referred patients. [11] In one study, researchers estimate the healthcare cost of IBS in the United States to be $8 billion per year. [12]

Patho-physiology of IBS

The cause of irritable bowel syndrome is unknown, though associated pathophysiology includes altered gastrointestinal motility and increased gut sensitivity. Some studies, [13, 14] but not all, [15] reported increased small-bowel and colonic contractions temporally associated with abdominal pain. Heightened sensitivity to visceral distention, particularly that which is perceived as noxious, has been described in numerous studies. [16, 17] Several theories have been proposed regarding the etiology of IBS of which the most important are as follows:

Altered responses of general stress circuits

The amygdala located in the CNS is known as an important structure active in the response to anxiety. This center activates the hypothalamic- pituitary-adrenal (HPA) axis
and the autonomic system when patients find themselves in anxious situations. Chronic anxiety increases the activity of the amygdala leading to the formation of an HPA axis which will ultimately cause induced visceral hyperalgesia.\cite{18,19} Visceral hypersensitivity is considered to be one of the main factors that cause symptoms in IBS sufferers and has been shown to play a key role in the pathophysiology of IBS.\cite{20}

The alternation of autonomic and neuroendocrine systems in response to visceral stimulation

In IBS sufferers an enhancement of their colonic sensitivity to factors such as infection, chronic inflammation, gastrointestinal (GI) micro-flora and impaired down regulation appears to be of importance in the pathogenesis of IBS. The enhancement of colonic sensitivity in response to stress, food, physical stimulation, CCK and corticotropin releasing factor (CRF) has been shown to be evident in individuals complaining of IBS.\cite{21} Changes have also been shown in intestinal motility, in the form of an increase in MMC, and retrograde duodenal and jejunal contractions.\cite{22-24} Numerous high amplitude contractions (HAPCS) seem to suggest an increase in IBS-D and reduction in IBS-C.\cite{25}

Serotonin

Serotonin is synthesized and released by enterochromaffin cells in the GI and plays an important role in regulation of GI motility, sensation and secretion. Excess released serotonin is mopped up by the serotonin reuptake transporter (SERT).\cite{26,27} Its physiological effects on IBS patients form the basis of two subtypes, namely 5HT3 and 5HT4,\cite{28} causing improvement in IBS-C patients\cite{29} while 5HT3 has an invert effect as an anti-diarrhea in IBS-D.\cite{30} Serotonin promotes its effects on the GI system through motility, secretion and visceral sensation; various studies have indicated the role of intolerance in the functioning of 5HT in the non-organic GI system, particularly in IBS following disturbances in the secretion and its reuptake. Several studies have indicated a noted imbalance in the functioning of 5HT due to an impairment in its release and
reuptake mechanisms by SERT in functional GI disorders which has in particular been shown to be true of IBS.\textsuperscript{[27,31]}

Low grade inflammation

One of the factors that have an important role in IBS is regulation of the immune system. This can be further alluded to by describing and analyzing its effects on GI infections, IBD and microbial flora.

Post-infectious IBS

Between 3 and 35\% of patients assessed progress on to develop IBS symptoms three to twelve months after suffering from GI infections.\textsuperscript{[32,33]} In particular, a rise in mucosal inflammatory cells, especially mast cells, in various parts of the small intestine and colon has been shown. An increase in the release of certain mediators such as nitric oxide, interleukin, histamine and protease leads to the stimulation of the enteric nervous system; such mediators eventually cause impairments in motility, secretion and hyperalgesia of the GI tract.\textsuperscript{[34]}

The role of bacterial flora in IBS

There are a limited number of bacteria such as Lactobacillus and Enterococci in the stomach and upper parts of the large intestine. However, the number of microorganisms shows a vast increase in the distal parts of GI system and can reach as high as $10^{12}$ per ml. Some studies claim that a relationship between the microbial flora of the gastro-intestinal tract and IBS may exist. Changes in the quantity and quality of bacteria present can convey selective effects on sensory-motor dysfunctions which can be influenced through bile acid malabsorption, mucosal irritation and inflammation, increased food fermentation and gas production.\textsuperscript{[35,36]} Increased fecal numbers of Lactobacilli, coliform and Bifidobacteria have been reported in patients affected by IBS,\textsuperscript{[37]} explaining the suggested use of probiotics in the treatment of IBS.

The role of genetic factors in IBS
The role of genetic factors influencing the prevalence of IBS has been shown in several studies. Family members of patients suffering with IBS may exhibit similar GI complaints. IBS has been shown to be twice as prevalent among monozygotic twins as compared with dizygotic twins. A down regulation in the control asserted by genetic polymorphisms and SERT in various studies is consistent with the notion of a significant role played by genetic factors. More recently studies conducted on twins have demonstrated controversial results as to the role of genetic factors in IBS. Some evidence shows that genetic factors can control the production of certain immunological factors such as T-helper 1, 2 ILs-4,6 and IL-10 which can affect individual susceptibility to post-infectious IBS. With the accumulation of more in depth knowledge of the pathophysiology of IBS important breakthroughs can be made in the subsequent treatment process.

Clinical manifestations of irritable bowel syndrome
Symptoms include both GI and extra intestinal complaints with the primary (main) GI syndrome portraying chronic abdominal pain and altered bowel habits.

Chronic abdominal pain
Abdominal pain is usually described as a sensation of cramps of varying intensity along with periodic exacerbations. The pain is usually located in the lower abdomen, often felt in the lower left quadrant.

Altered bowel habits
By definition, patients suffering with IBS often complain of altered bowel habits; this can be observed in the volume, frequency and consistency of the patient’s stools.

Diarrhea
Diarrhea is usually characterized as frequent loose stools of small to moderate volume. Stools generally occur during the hours in which patients are awake; frequently in the morning or after mealtimes. Most bowel movements are preceded by lower abdominal cramps (tenesmus), urgency to defecate and often fecal incontinence is perceived which
may be followed by a feeling of incomplete defecation. Approximately half of all patients suffering with IBS complain of a mucosal discharge occurring along with their stools. Large volume diarrhea, bloody stools, nocturnal diarrhea and greasy stools are not associated with IBS, but rather suggest an organic disease instead. A subgroup of patients displays an acute viral or bacterial gastroenteritis known as post infectious IBS.

**Constipation**

Stools are often hard and may be described as being pellet shaped. Patients may experience a sense of incomplete evacuation occurring even when the rectum is completely empty. This can lead to long periods of time spent in the bathroom.

**Other GI symptoms**

Upper GI symptoms include gastro-esophageal reflux, dysphagia, early satiety, intermittent dyspepsia, nausea and non-cardiac chest pain are noted as being common. Patients may also frequently complain of abdominal bloating and an increase in gas production in the form of flatulence or belching.\(^{[49]}\)

**Extra-intestinal symptoms**

These include impaired sexual function, dysmenorrhea, dyspareunia and an increase in the frequency and urgency to urinate. Patients are more likely to suffer from hypertension, asthma or fibromyalgia.\(^{[50,51]}\)

**Diagnosis of irritable bowel syndrome**

The definitive diagnosis of IBS has proved extremely difficult. Traditionally, IBS has been diagnosed via a process of exclusion of other clinically defined illnesses. As such, no specific or unique organic pathology has been consistently demonstrated in IBS. There has been an ever increasing desire to create diagnostic protocols due to the large cost burden and numerous patient referrals to GI clinics. The probability of indiscrimination of important and treatable diseases such as Crohn’s, colon cancer and the unwillingness of physicians to use para clinic methods in diagnosis has also added to this desire. Valid criteria that could lead to a positive diagnosis without the need for extensive and
expensive testing have been examined. Such criteria included the Manning Criteria that initially introduced a questionnaire which was given to 109 randomly selected patients referred to gastroenterology clinics with complaints of abdominal pain, changes in bowel habits or both in order to identify the presence of symptoms thought to be typical of IBS. A review of the case records established a definite diagnosis of IBS in 32 and of organic disease in 33 of the 109 patients that completed the questionnaire. It was concluded that a thorough case history can increase diagnostic confidence and reduce testing costs in many patients with chronic abdominal pain. Subsequently, the total number of symptoms recorded in the questionnaire were modified and reduced from 15 to 6 criteria.\textsuperscript{[52-55]} In 1980, The Rome I criteria was proposed by a working team as a new diagnostic guideline and upon use was found to be more valuable than previously established criteria.\textsuperscript{[56]} Utilizing new methodology, the Rome II Criteria which was a modified version of the Rome I Criteria was proposed by the Rome Working Team; in this method specific questions regarding diarrhea and constipation were removed.\textsuperscript{[57]} Later, in 2006, the Rome III Criteria has been further specifically defined by an expanded Rome Working Team to include the following modifications to the Rome II Criteria.\textsuperscript{[58]}

i) The introduction of a frequency threshold relating to symptoms required to meet criteria (recurrent abdominal pain or discomfort for at least three days per month in the previous three months),

ii) The duration of symptoms was reduced from a period of twelve to six months

iii) The necessity to refine IBS sub-typing regarded as sufficient for diagnostic purposes.

The recommended course of action for patients with intermittent abdominal pain and changes in bowel movements are:

i) Evaluation of the patient to establish whether or not they meet the established Rome criteria,
ii) Paying particular attention to warning signs as an indication for conducting para-clinical testing in order to rule out infectious etiologies,

iii) Serological testing of patients who exhibit apparent symptoms of diarrhea and bloating in the absence of warning signs to rule out celiac disease and

iv) Upon a negative serological test result, patients are ultimately diagnosed and treated for IBS with a recommendation that cases be followed-up after a period of six weeks.
Flowchart 1: Diagnostic Algorithm of IBS

1. Frequent abdominal pain (on average, >1 attack/month, fluctuating course)
2. Relief of abdominal pain after defaecation
3. Loose or harder stool with onset of abdominal pain
4. Altered bowel frequency with onset of abdominal pain
5. Abdominal distension
6. Passage of mucus per rectum
7. Sensation of incomplete evacuation

Any alarm features such as:
- bleeding per rectum
- steatorrhoea
- weight loss
- fever
- nocturnal symptoms
- onset at age > 40
- recent onset
- progressive course
- family history of colon cancer (especially at young age)
- abnormal sign on examination

Simple investigations:
- Full blood counts
- Erythrocyte sedimentation rate
- Thyroid function test
- Stool occult blood, leukocytes, culture, ova and cyst

All investigation results normal

IBS more likely

Organic GI (especially colonic) disease more likely

Investigate along the line of organic GI disease

Investigation results abnormal

Review diagnosis in 6 to 12 weeks, if no improvement with treatment, consider referral to specialist
Management of IBS

IBS is characterized by a variety of chronic symptoms that include abdominal pain, an alteration in bowel habits and flatulence. The disorder has no definitive treatment but could be controlled by eliminating of some exacerbating factors such as certain drugs, stressor conditions and changes in dietary habits. Hidden drug addiction should be considered as well.\textsuperscript{[59]}

Non-pharmacologic management

The treatment goal in patients suffering with IBS is to reduce their overall symptoms and a subsequent effort should be made to try and eliminate or decrease the patient's primary symptoms which should be addressed on first encounter with the patient. Some recommendations should be put forward to the patients regarding their dietary habits. It should be noted that the intake of foods does not cause IBS; however the contact of food with the GI tissues can convey various effects in individuals suffering from IBS through various immunologic, physiologic and biochemical mechanisms.

Dietary modification

A high-fiber diet helps to prevent both excessive hydration and dehydration of stool. Clinical trials have also demonstrated placebo responses of 63% to 71% in patients with IBS who used different fiber preparations.\textsuperscript{[60]} Thus, a trial of fiber seems appropriate in all patients with IBS given the large placebo response and safety profile. Gradual introduction of fiber may diminish the common complaint of gas and bloating from these agents.\textsuperscript{[61]}

Psychosocial treatments

Since anxiety and depression are the most prevalent psychologic conditions among patients affected by IBS, behavioral treatments may be considered in the IBS patients who have associated stress symptoms. Hypnosis, biofeedback and psychotherapy can help to alleviate anxiety levels in these patients.\textsuperscript{[62-68]} It has been shown in studies that physical treatments such as massage therapy and acupuncture may help to reduce
symptoms and emotional signs.\textsuperscript{[69]} Although this is not conclusive, as other studies have shown that the efficacy of acupuncture is the same as placebo.\textsuperscript{[70]}

Pharmacologic management

Treatment of IBS is based on the main symptoms of the disease such as diarrhea, constipation, abdominal pain or bloating.\textsuperscript{[71]} Determination of disease severity and the patient’s major symptoms are deemed as being the main goals of treatment.

Antispasmodics

Antispasmodics are thought to relieve abdominal pain by reducing intestinal smooth muscle contractions.\textsuperscript{[72,73,74,76]} The published reviews assessing the efficacy of antispasmodics in IBS patients have yielded conflicting summaries.\textsuperscript{[77, 74-79]} Some of the reviews included up to eleven different antispasmodic agents – however, only three of these are available in Canada with an official indication for irritable bowel syndrome: dicyclomine \textit{BENTYLOL}, pinaverium \textit{DICETEL} and trimebutine \textit{MODULON}.\textsuperscript{[80,81]} Therefore, these medications may be trialed empirically in patients suffering from abdominal pain. They can be used as-needed for acute attacks of abdominal pain or scheduled before meals in patients with postprandial symptoms.\textsuperscript{[73]} Use with caution in patients with constipation, as antispasmodics may worsen this symptom.

Anti-depressant drugs

Amitriptyline is one of the tricyclic antidepressant drugs commonly used in the treatment of IBS patients at low doses (10mg per day).\textsuperscript{[82]} Effects of this drug include visceral hyperalgesia, sleep improvement and normalization of intestinal transient time. When used in high doses (e.g., 100 mg or more at bed time) it may help to relieve depression and anxiety.\textsuperscript{[83]} Two meta-analyses have shown that low to moderate doses of TCAs were more effective than placebo in relieving pain and general symptoms of IBS sufferers,\textsuperscript{[84,85]} however a third meta-analysis rejected the previous findings and reported that TCA anti-depressants were no more effective than placebo. Some studies have shown that SSRI's have beneficial effects on patients affected by IBS,\textsuperscript{[86]} and according
to other studies these drugs are deemed effective in reducing abdominal pain relief in such patients.\cite{84} SSRI’s are effective pain relievers and reduce others symptoms such as fibromyalgia.\cite{87,88}

**Probiotics and antibiotics**

Probiotics or non-absorbable antibiotic (lactobacilli, bifidobacteria, VSL#3 and rifaximin) have been tried in IBS to try to alter the intestinal micro-flora, hopefully to reduce visceral hypersensitivity. The improvement for global symptom control is controversial but individual symptoms like bloating, flatulence or pain may respond. Probiotics have a beneficial effect on intestinal mucosa via several proposed mechanisms that include suppression of the growth and binding of pathogenic bacteria, improvement of the barrier function of the epithelium, and alteration of the immune activity of the host.\cite{89,90} Probiotics secrete short chain fatty acids, an action that results in decreased luminal pH and production of bactericidal proteins.\cite{90} Butyric acid, a byproduct of bacterial fermentation of fiber, has been shown to nourish colonic enterocytes, enhancing mucosal integrity.\cite{91,92} The DNA of probiotic organisms has also been shown to inhibit apoptosis of epithelial cells\cite{93,94} In addition, probiotics may improve bowel dysmotility. Confirmatory studies in the future are awaited. Furthermore, one recent study has suggested that rifaximin may be effective in the prevention of post-infectious IBS.\cite{91}

**Herbal medicine**

Well conducted trials from Australia and Germany have shown that specific types of herbal medicine significantly improved symptom scores when compared to placebo group. The underlying mechanism is, however, uncertain as there are numerous components in the herbal medicine and further studies are awaited.\cite{95}

**Selective Serotonin Reuptake Inhibitor (SSRI)**

In patients suffering from IBS-related abdominal pain and constipation may benefit from a SSRI. The SSRIs have also been investigated in patients suffering from diarrhea-predominate IBS. However, until additional evidence is available, reserve this class of
antidepressants for co-morbid mental health disorders in these patients. Only three SSRI antidepressants have been studied in IBS patients to date – fluoxetine PROZAC, paroxetine PAXIL and citalopram CELEXA. 

Management of IBS with concomitant bloating

Abdominal bloating, a symptom commonly witnessed in IBS patients, is often observed in constipation predominant IBS patients. Probable mechanisms of bloating may include:

i) Psychosocial,

ii) Weak abdominal muscles,

iii) Paradoxical relaxation of abdominal muscles and

iv) Changes in visceral sensitivity.

Antibiotics are effective in the improvement of bloating symptoms. In cases where bacterial overgrowth has arisen, antibiotic treatment may be effective. Short-term antibiotic treatment is recommended to help improve bloating symptoms in IBS patients. The use of non-absorbable antibiotics such as rifaximin leads to relief from symptoms of discomfort and bloating in IBS patients. Short term use of rifaximin has been demonstrated to reduce bloating but relapse is often frequent. In a placebo controlled study, prescribing SSRI’s such as Citalopram and Fluoxetine led to relief from bloating. These drugs may also convey anti-anxiety and anti-depressive effects. A plant extract that contains Coriandrum sativum and Mentha spicata has been shown to reduce bloating in IBS patients, as compared to placebo. This is probably achieved via its antispasmodic effects.

Management of IBS-diarrhea predominant

In this group of patients, anti-diarrheal agents are generally effective but few clinical trials have been conducted for confirmation. There is evidence which suggests that the use of regular low doses of anti-diarrheal agents (e.g., Loperamide every morning or BD) could be effective in such patients. A major double blind clinical trial has been
conducted on diarrhea predominant IBS patients using Alosetron (5-HT3 antagonist receptor) in doses of 1 mg, twice daily for a period of 12 weeks. A reduction in the frequency and urgency of defecation, along with reduced abdominal pain and IBS symptoms have been shown, which will in turn help to improve the patient’s quality of life. The FDA has restricted the use of this drug to females affected by IBS who display major diarrheal symptoms. Due to some adverse effects such as ileal obstruction, intestinal obstruction, rectal fecal impaction, intestinal perforation and ischemic colitis the use of this drug has subsequently been restricted by the FDA.

Anti-depressants are effective in controlling abdominal pain and leading to diarrheal relief in diarrhea predominant IBS patients. TCA’s are able to increase colon transit time through anti-cholinergic effects and may be useful in patients suffering predominantly from diarrhea. Probiotics have also been proven to be useful in diarrhea predominant IBS sufferers. A review of epidemiologic studies suggest the prevalence of IBS in Iran is among the lowest reported in neighboring developing countries and the Asian region, and is more common in females than males. For disease diagnosis, a careful history, physical exam and laboratory tests based on symptoms along with simultaneous observation of warning signs is very important. In these patients, the main goal is education and reassurance. Recommendations about dietary habits and drug therapy based on the primary IBS symptoms are recommended. Dietary changes should not disrupt the patient’s quality of life.

Management of IBS-constipation predominant

Constipation is said to be a non-specific symptom witnessed in patients who possess an abnormal colon transient time or defecation disorder with an increase in straining. In such patients treatment modalities are as follows:

The intake of fiber is highly recommended. Often consumption of roughly 12 grams of fiber daily has been shown to be relatively effective in reducing symptoms although this effect is not regarded as being more than the effect that a placebo offers.
laxatives are predominantly used for the treatment of constipation. Although no specific clinical trials on IBS patients have been conducted, yet fiber supplements are used in the treatment of constipation. This may cause an increase in bloating that often occurs as a side effect. Long-term use of osmotic laxatives has been proven to be safe and effective. Magnesium, phosphate and emollients containing polyethylene glycols have also been shown to be efficient as well.

CONCLUSION

New concepts on the pathophysiology of IBS are based on abnormalities in the central and autonomic nervous system and visceral hypersensitivity. Emerging new mechanisms of both peripheral and central origin have shown that IBS is actually a very heterogeneous condition. There is sufficient evidence to conclude that IBS is an important medical disorder with significant impact on those afflicted with regard to symptom severity, disability, and impaired quality of life. Furthermore, the burden to society in terms of direct health care costs and indirect effects including work absenteeism exceeds that of most GI disorders. Advances in the field are exciting and hopefully would lead to improvement in the management of IBS patients.

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