Irritable Bowel Syndrome: a Review

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Abstract

Irritable bowel syndrome (IBS) is the most common disorder encountered by gastroenterologists. It has a substantial global burden and is associated with significant disability and high costs. It adversely affects the health related quality of life of large population worldwide. A lot needs to be explored regarding the diagnosis, pathophysiology and treatment of this ailment. In order to alleviate this syndrome various new approaches are being tried to be used either alone or in combination with existing therapies. Its prevalence is found to be more in developed countries, and more in women than men. IBS is a disorder which is often missed by physicians and also suffers the ignorance of patients. Thus it becomes increasingly important to address this problem and develop new approaches to decrease the worldwide burden of this disease. This article tries to discuss the available strategies and the future frontiers regarding IBS, ranging from diagnosis to treatment.

Key words: Diagnosis, global burden, pathophysiology, strategies, treatment
Introduction

Irritable bowel syndrome (IBS) is a chronic functional gastrointestinal disorder (FGID) characterized by abdominal pain or discomfort, bloating, and altered bowel habits. It involves a broad range of physiological and psychological changes that influence brain-gut regulation, gut function, visceral perception, and mucosal integrity and function (Camilleri et al., 2008). IBS shows a chronic course in which phases of remission of variable length are interrupted by acute episodes. FGID basically comprises several variable combinations of chronic or recurrent gastrointestinal (GI) symptoms that cannot be explained by structural or biochemical abnormalities. Most frequently occurring and investigated FGIDs are IBS, dyspepsia, constipation, and oesophageal disorders. The most accepted criteria for classification of FGIDs is ‘Rome diagnostic criteria’ (Corazziari, 2004). This criterion has been revised time and again, Rome III version being the current one.

Although IBS has been regarded as a non-organic problem, there are various recent studies which suggest the presence of an organic component in IBS. Under the light of these studies, the term functional applied to IBS will not be correct. However, this view is controversial and various researches are being carried out.

Prevalence

Prevalence of IBS has been found to increase with industrial growth and development, with developed nations showing greater occurrence than developing nations. Values for prevalence in developing nations such as India (4.2%) have been found to be very low compared to developed nations such as North America (10-15%) (Saito et al., 2002). Whether or not gender affects IBS prevalence is still controversial. Female gender is frequently reported as a risk factor for developing post-infection IBS. This may be partly due to confounding with anxiety and depression which is common in women, since when this was controlled for in multivariate analysis female gender was no longer a risk factor (Dunlop et al., 2003). Recent Department of Gastroenterology and Human Nutrition and Centre for Community Medicine reported that the prevalence of IBS varies from 4% to 20% in different Asian nations. The prevalence of IBS in a North Indian community is 4% (Makharia et al., 2011). IBS poses a significant burden on the rural adults.

Quality of life and Burden

Health-related quality of life (HRQOL) addresses the psychologic, social, and physical consequences associated with a particular disease. IBS has chronic and unsettling symptoms with large unmet medical needs thus have negative impact on patient’s quality of life. Patients with IBS who seek medical attention typically have HRQOL that is substantially worse in depressed patients with suicidal ideation (Agarwal et al., 2011). IBS produces individual as well as social burden, greatly influencing the well-being and economics. In a survey of 789 IBS patients conducted by National Health and Wellness Survey, U.S., IBS was associated with poorer HRQOL, greater work productivity loss and activity impairment, and greater healthcare resource use (DiBonaventura et al., 2011). IBS also has a negative impact on patients’ activities of daily living, work, and leisure time. It may affect sleep, diet, ability to travel, and sexual function, as well as personal relationships with family and friends and work-related roles.

The annual cost of IBS treatment in the United States has been estimated to be between $1.7 billion and $10 billion in direct medical costs, excluding prescription and over-the-counter (OTC) drug costs (i.e., primary and specialist physician visits, outpatient care, and diagnostic testing) (Sandler et al., 2002) and up to $20 billion in indirect costs (e.g., productivity loss) (Bethesda, 2001). In an analysis of four data sources (National Ambulatory Medical Care Survey, National Disease and Therapeutic Index, National Hospital Discharge Survey, and National Inpatient Sample), 45.3% of physician office visits attributable to IBS were scheduled with gastroenterologists. From these same data sources, it was estimated that 80,000 to 100,000 patients are hospitalized for IBS-related treatment each year in the United States (Shih et al., 2002).
Diagnosis

Symptom based criteria

IBS has historically been viewed by many as a diagnosis of exclusion rather than as a primary diagnosis. First symptoms based criteria to be universally accepted was Manning criteria in 1978. It was found to be equally applicable to African-American populations as well as white (Lacy et al., 2009). However studies have shown it may not prove to be an ideal instrument for diagnosis in male and shows gender difference (Smith et al., 1991). Following this, in an attempt to improve the existing criteria, Rome I criteria came in 1990. This was subsequently revised in 1999 to formulate more useful Rome II criteria. However the role of Rome II in routine clinical practice remains poorly defined. It is clear that a percentage of patients who do not fulfill the Rome II criteria eventually are given a diagnosis of IBS, typically after exclusion of organic gastrointestinal disease following detailed diagnostic testing. Further modifications were done and in 2006 Rome III criteria was formulated. These criteria are summarized in Table 1.

Table 1: Symptom based Criteria’s for IBS

<table>
<thead>
<tr>
<th>Manning criteria</th>
<th>Rome criteria I</th>
<th>Rome criteria II</th>
<th>Rome criteria III</th>
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<tr>
<td>Abdominal pain that is relieved with a bowel movement.</td>
<td>Continuous or recurrent symptoms of abdominal pain, relieved with defecation, or associated with change in frequency or consistency of stool; and/or Disturbed defecation (two or more of): Altered stool frequency Altered stool form (hard or loose/watery) Altered stool passage (straining or urgency, feeling of incomplete evacuation), Passage of mucus usually with Bloating or feeling of abdominal distension.</td>
<td>At least 12 weeks or more, which need not be consecutive, in the preceding 12 months of abdominal discomfort or pain that has two out of three features: Relieved with defecation and/or Onset associated with a change in frequency of stool; and/or Onset associated with a change in form of stool.</td>
<td>Recurrent abdominal pain or discomfort at least three days per month in the past three months with two or more of following: • Improvement with defecation; and/or • Onset associated with a change in frequency of stool; and/or • Onset associated with a change in form of stool.</td>
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**Diagnostic criteria**

American Gastroenterological Association (AGA) position statement on IBS states that, in the absence of ‘alarm features’ or ‘red flags’ and/or any positive screening studies from referring physicians, additional diagnostic testing is not typically necessary. Red flags or alarm features include symptom onset after age 50, severe, unrelenting diarrhoea, nocturnal symptoms, unintentional weight loss, haematochezia, or a family history of organic gastrointestinal diseases such as IBD, celiac sprue or malignancy. For patients with a short duration of symptoms, demographic features such as older age at symptom onset, a family history of organic gastrointestinal disease, or a lack of concurrent psychosocial difficulties or symptom behaviours, then a complete blood count (CBC) and occult blood (FOBT) are recommended for screening purposes. Additional tests such as erythrocyte sedimentation rate (ESR), serum chemistries, and stool examination for ova and parasites (O&P) should be individualized, based upon symptom pattern, geographic area, and relevant clinical features such as predominant diarrhoea. These evaluations are intended to rule out organic gastrointestinal diseases such as IBD, colorectal cancer and infectious diarrhoea. Other experts also recommend the use of hydrogen breath tests and thyroid function testing to rule out lactose malabsorption and thyroid dysfunction, respectively.

**Blood tests**

Several studies have examined the role of blood tests in IBS. They include tests such as CBC, serum chemistries, serological screening for celiac sprue, thyroid function tests. Tolliver *et al.* has recommended the omission of ESR and thyroid testing as part of routine blood tests for IBS patients (Tolliver *et al.*, 1994). Thus it can be concluded that evidences does not support the routine use of blood tests to exclude organic gastrointestinal disease in patients who present with typical IBS symptoms without alarm features.

**Stool tests**

As a conclusion of various studies the fact that can be briefed about stool tests is that they are not strong enough to rule out the possibility of organic gastrointestinal disease in patients who present with typical alarm symptoms. Tolliver *et al.* also concluded that testing for ova and parasites should be conducted only when parasites have been in an area known to be endemic for parasites (Tolliver *et al.*, 1994). Selected application of stool testing for O&P and/or *Giardia lamblia* antigen should be considered in patients at greater risk for such infections.

**Hydrogen breathe testing**

Lactose malabsorption is typically diagnosed via abnormal hydrogen breath testing. The studies of Tolliver *et al.* suggest a role for routine testing of patients for sugar malabsorption as part of an overall evaluation for IBS (Tolliver *et al.*, 1994). However, these studies were performed in areas where the population consisted of many people known to be at risk for lactose intolerance (southern Alabama and Spain, respectively) (Tolliver *et al.*, 1994).

**Flexible sigmoidoscopy and Colonoscopy**

Study carried out by MacIntosh *et al.* showed that routine rectal biopsies were a costly and unnecessary undertaking in the evaluation of patients with presumed IBS (MacIntosh *et al.*, 1992). One weakness of this study is that patients with constipation predominant and alternating constipation/diarrhea of IBS symptoms, along with patients who had diarrhea-predominant IBS, were included in the study, perhaps underestimating the usefulness of rectal biopsy in diarrhea-predominant IBS population.

**Imaging studies**

Use of imaging studies has also been a controversial issue. In a study carried out by Francis *et al.*, authors concluded that using Rome criteria to achieve a positive diagnosis of IBS was a safe practice and that routine use of ultrasound of the abdomen in patients suspected of IBS was unnecessary (Francis *et al.*, 1996). In another study carried out by Hamm *et al.*, colonic abnormalities were detected in only 2% of the patients, thus concluding that colonic imaging added little to the differential diagnosis of IBS (Hamm *et al.*, 1999).

Thus it can be concluded that the diagnosis of different types of IBS (Fig. 1) is largely based on
Rome criteria following the exclusion of organic diseases of GI tract. To further improve the diagnosis various arenas including psychological rating scales, physiological recordings, imaging studies, morphological data and behavioural outputs in addition to genomic, proteomic or metabolomic approaches are also being considered so as to develop a holistic biomarker technique for diagnosis of IBS.

**Pathophysiology**

The mechanism associated with functional gastrointestinal disorders are complex, several hypothesis have been put forth to explain the brain gut dysfunction, including abnormal motility, visceral hypersensitivity, inflammation and infection, neurotransmitter imbalance and psychosocial factors (Fig. 2).

**Abnormal motility**

Various symptoms associated with IBS including abdominal pain, bloating, altered bowel habits can result due to abnormal motility. It has been observed, motility pattern are qualitatively similar in IBS patients and healthy individuals, and however responses to various stimuli is exaggerated in case of IBS patients. Reduced high amplitude propagated contractions in the left colon are associated with constipation and increased fasting contractions and rapid colonic transit in the proximal colon have been linked to diarrhoea (Drossman et al., 2002).

**Visceral hypersensitivity**

Visceral stimuli from the GI tract are transmitted via afferent nerves through spinal cord to the brain where sensations such as pain are perceived (Drossman et al., 2007). Reports claim 80-90% incidence of visceral hypersensitivity in IBS (Bouin, 2006). Patients with IBS shows enhanced perception throughout the GI tract, including the oesophagus, stomach, duodenum and ileum. The hypersensitivity due to accentuated response in the brain of IBS patients could be from increased peripheral sensitivity to stimuli from GI tract, amplification of signals during processing through the spinal cord and brainstem, or a central mechanism with signal amplification that occurs in brain.

**Inflammation and infection**

Post infection IBS refers to sudden onset if IBS symptoms after a bout of gastroenteritis in individuals with a previously healthy GIT. In a minority of these cases these symptoms do not resolve and patients go on to develop chronic IBS symptoms that can account for 6-17% of the general IBS population. Another study has also shown that the bacterial overgrowth in the small intestine may also play a role in IBS (Lin, 2004). Inflammation of the enteric mucosa or neural plexuses may initiate or contribute to symptoms of IBS (Rossel et al., 1999). An increased number of mast cells in the muscularis externa of the colon and the ileal and colonic mucosa have been reported in some studies (Weston et al., 1993).

**Neurotransmitter imbalance**

Enteric nervous system functions semi autonomously, it responds directly to signals from effector systems, such as smooth muscles, endocrine cells and blood vessels, as well as from autonomic input through parasympathetic and sympathetic nervous system (Atkinson et al., 2006). GI homeostasis is maintained by equilibrium between the pathways that enhance and those that inhibit secretion and motility. Failure in this equilibrium results in various symptoms of IBS.

Various neurotransmitters (eg. serotonin, norepinephrine, dopamine, acetylcholine, glutamate), neuropeptides (eg. substance P, vasoactive intestinal peptide, calcitonin gene-related peptide), and other neuromodulators (eg.
neurotrophic factors) are present in both the brain and the gut. There is growing evidence that a serotonergic mechanism may be involved in the pathophysiology of IBS. 5-HT excess is considered to be responsible for symptoms of diarrhoea dominant IBS (IBS-D) and insufficient release of 5-HT being responsible for the symptoms of constipation dominant IBS (IBS-C). Findings supporting this school of thought includes:

- Increased postprandial levels of circulating 5-HT in subjects with IBS-D;
- IBS-D subjects were observed to have elevated platelet-depleted plasma 5-HT levels in fasting and fed states;
- The mucosal 5-Hydroxyindoleacetic acid (5-HIAA)/5-HT ratio was decreased in subjects with IBS-C;
- A lack of increase in plasma 5-HT levels after meal ingestion in those with IBS-C (Dunlop et al., 2005).

**Fig. 2:** Mechanism of control of pain, gastrointestinal motility and secretion.
Management of IBS

Dietary therapy

Introduction of fibres in the diet helps to firm up stool in case of IBS patients having diarrhea predominance. Fibre supplements may be better tolerated but need to be started at a low dose and built up slowly because of the increase in bloating that often occurs with their use. *Psyllium* has been used as fibre supplement (Chang et al., 2010). Immunoglobulin G (IgG) mediated hypersensitivity remains controversial. One study reported the effectiveness of an elimination diet based on IgG antibodies (Atkinson et al., 2004). There is a certain group of IBS patients (described with latent or potential celiac disease) which appear to respond to gluten free diet (Wahnschaffe et al., 2007).

Fermentable oligosaccharides, disaccharides, monosaccharides and polyols (FODMAPs) are thought to exert an osmotic effect that results in putative luminal distension (Gibson et al., 2010). Low FODMAPs diet is reported to reduce severity of IBS symptoms.

Antispasmodics

Anticholinergic agents may provide temporary relief from painful cramps related to intestinal spasm. These are drugs are more effective when taken in anticipation of predictive pain. They inhibit the gastrocolic reflex. Usually they are given 30 minutes before meal so as to achieve optimum concentration before the anticipated pain onset. Belladona alkaloids containing antispasmodics may cause xerostomia, urinary hesitancy and retention, blurred vision and drowsiness. Thus some physicians prefer synthetic anticholinergicics such as dicyclomine that produce fewer side effects.

Antidiarrheal agents

If diarrhoea is a predominant problem, loperamide is useful and will reduce diarrhoea, but will not alter abdominal pain or other IBS symptoms over placebo based on the current published reports (Quartero et al., 2005). Intestine does not become tolerant of antidiarrheal effect of opiates and thus increasing dose is not required. They should be taken before the onset of anticipated pain. Antidiarrheals are temporary treatment and needs to be withdrawn with substitution of high fibre diet.

Antiflatulence therapy

Patients are advised to eat slowly. Also certain eatables and drinks are avoided, such as chewing gums, carbonated beverages, artificial sweetners, legumes and food of cabbage family. Simethicone, antacids and activated charcoal have also been tried but are not much effective.

Antidepressant agents

Tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs) are considered for the treatment of IBS because of their hyperalgesic effect (Ford et al., 2009). In diarrhea predominant IBS patients, the tricyclic antidepressants imipramine slows jejunal migrating motor complex transit propagation and delays orocecal and whole gut transit, indicative of motor inhibitory effect. SSRI paroxetine accelerates orocecal transit, raising the possibility that this drug class may be useful in constipation predominant patients. A systematic review and meta-analysis that examined the efficacy of TCAs and SSRIs in the treatment of IBS reported that both drug classes were equally effective in improving IBS symptoms (Gershon, 2004).

Serotonin receptor agonists and antagonists

5-HT<sub>3</sub> receptor antagonists – 5-HT<sub>3</sub> receptors are expressed on subsets of neurons intrinsic to the enteric nervous system including intrinsic primary afferrent neurons (IPANs), as well as on extrinsic primary afferents (EPANs; both spinal and vagal afferents). 5- HT<sub>3</sub> receptor antagonists are thought to interfere with 5HT signaling to IPANs, thereby attenuating peristaltic and the secretomotor reflexes, and in turn decreasing intestinal motility and secretion (Watson et al., 2001). Alosetron have been shown to improve quality of life in IBS-D affected women (Gershon et al., 2007). Alosetron was withdrawn from market in 2000 and reintroduced in 2002 under restrictive guidelines by the US food and Drug administration (FDA) due to serious adverse effects including severe constipation and ischemic colitis. Currently it is approved to be used in female patients with refractory and severe symptoms of IBS-D; the drug is absolutely contraindicated in constipation.

5-HT<sub>4</sub> receptor agonists - Clinical and preclinical evidences suggest that serotonin via 5-HT<sub>4</sub> receptors modulate gastrointestinal motor...
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function, in particular the peristaltic reflex. They exhibit prokinetic activity. Tegaserod, a 5-HT₄ receptor partial agonist has been approved for the treatment of constipation-predominant IBS. 5-HT₄ receptor is involved in the modulation of visceral afferent function. Presumably by facilitated release of acetylcholine via presynaptic 5-HT₄ receptor on cholinergic neurons, tegaserod accelerates upper and lower gut transit in healthy subjects, promotes gastric emptying, small bowel and colonic transit in constipation-predominant IBS (IBS-C) patients, and increases faecal water and intestinal secretion in female subjects (Gershon et al., 2007). From earlier reports it has also been known that in freshwater pollution, the toxicants are mostly introduced into the water bodies through anthropogenic activities such as industrial, agricultural, domestic, and urban activities (Obiakor et al., 2012). The post marketing analysis showed higher cerebrovascular and cardiac events, leading to the removal of tegaserod from the use in USA market in 2007 (US FDA, 2010). Another 5-HT₄ receptor agonist prucalopride has demonstrated significant promise in clinical trials in the treatment of IBS-C, the drug is now approved in Europe for the treatment of refractory constipation in women (Tack et al., 2009).

5-HT₄ receptor agonist/5HT₃ receptor antagonist - As the category expects, this combination may be superior to each individual approaches. Renzapride is such a compound, and is developed for the treatment of IBS-C with an expected prokinetic effect because of its 5-HT₄ receptor agonist action. However it has not been found to be significantly efficacious in the treatment of IBS (Ford, 2010).

γ-Aminobutyric acid analog

Pregabalin is a novel second generation α₂δ ligand that is structurally similar to γ-aminobutyric acid (GABA), and is believed to decrease depolarization-induced calcium influx at nerve terminals, and thereby inhibit release of excitatory neurotransmitters by acting on the α₂δ auxiliary proteins associated with voltage-gated calcium channels. Its potential role in IBS is based upon a recent study demonstrating normalization of rectal distension sensory thresholds in IBS patients with rectal hypersensitivity (Houghton et al., 2007). Placebo-controlled trials of pregabalin for IBS are currently ongoing.

Agents acting on chloride channels in GI tract

GI tract contain various chloride channels that regulates the transport and secretion of fluids.

Type-2 chloride channels (CIC-2) - They are located on apical cell membrane of intestine. Activation of these channels causes an efflux of chloride ions into the lumen of GI tract, in order to maintain isoelectric balance, efflux of sodium ion occur subsequently. With this water also moves in lumen to maintain the isotonic environment via the paracellular pathway. This results in an increase in intestinal secretion and fluid volume, this offers a new therapy in the treatment of IBS-C and chronic constipation. Lubiprostone is an activator of CIC-2 channels and is currently approved by FDA for the treatment of IBS-C in women.

Cystic fibrosis transmembrane regulator (CFTR) chloride ion channels - They are found on the luminal membrane of enterocytes and have antisecretory action. Crofelemer, a CFTR chloride ion channel inhibitor has shown promising results in treatment of IBS-D (Tradtrantip et al., 2010). Linaclotide is an activator of CFTR chloride ion channels and is being evaluated for its potential for IBS-C treatment, with encouraging outcomes (Lembo et al., 2010).

Agents modulating intestinal flora

Dysequilibrium within microbiota is theorized to play a part in the pathogenesis of IBS (Parkes et al., 2008).

Probiotics - Their role and exact mechanism of action in IBS is not fully understood, but multiple hypotheses have been proposed. These include: adherence to the intestinal epithelium prevents pathogenic bacteria from accessing the intercellular space and subsequent invasion; production of antimicrobial substances that prevent invasion by pathogenic bacteria; alteration of the intestinal microflora may have effects upon intestinal motor and secretory functions; and generation of signals within the epithelium that modulate luminal immunity and thereby the inflammatory response of the GI tract (Brenner et al., 2009). *Bifidobacteria* and *Lactobacilli* species have been shown to improve IBS symptoms (Quigley, 2008).
Prebiotics - These are typically selectively fermentable oligosaccharides or more complex saccharides which when combined with probiotics help to augment their effects (Preidis et al., 2009). A trial involving fructo-oligosaccharides reported an associated decrease in the treatment of IBS (Paineau et al., 2008).

Antibiotics - Rifaximin, a gut-selective non-absorbable antibiotic with broad antimicrobial activity to include gram-positive and gram-negative aerobes and anaerobes (Jiang et al., 2005), has demonstrated the most promise in the treatment of IBS. In one randomized, double-blind, placebo-controlled study, rifaximin therapy was found to result in greater improvements in IBS symptoms over the ten-week follow-up period. Furthermore, those who received rifaximin also had improvements in their bloating scores after treatment (Pimentel et al., 2006).

Acupuncture (Lembo et al., 2009), hypnotherapy (Webb et al., 2009) and psychological therapies (Zijdenbos et al., 2009) are some of the other therapies use to relieve symptoms of IBS patients. A diagrammatic view of the various affected pathways and agents acting over them in IBS has been shown in Fig. 3.

**Fig. 3:** Various affected pathways and agents acting over them in IBS.
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Researches and clinical trials are also being carried out on development of newer strategies using new class of drugs including endocannabinoid system (Akbar et al., 2009), transient receptor potential vanilloid type 1 (TRPV1) (Akbar et al., 2009), β3 adrenoreceptor agonist (Cellek et al., 2007), neurokinin antagonists (Camilleri, 2010), corticotrophin releasing factors (Tache et al., 2009) for the management of visceral hypersensitivity; protease activated receptors (PAR) (Bradesi, 2009) having potential roles in visceral hypersensitivity and inflammation; cholecystokinin antagonists to stimulate GI motility (Cremonini et al., 2005).

Conclusions

IBS is often missed by health care providers and a diagnosis may be established only after other, more serious disorders have been excluded. There is dire need to develop new diagnostic strategies as presently available techniques are not complete sensitive in the sense to diagnose a patient and also the hallmarks signs and symptoms of IBS are neither sensitive nor specific for this disorder. Development of suitable biomarkers is of utmost importance. Another challenge with IBS is the tremendous variability in symptoms, which are frequently sustained over a short term (i.e. weeks or months), but the presence and severity of symptoms tend to wax and wane over a longer period (i.e. years). This affects patients health related quality of life and places tremendous burden over individual and society both economically and health wise. Thus, it is required that apart from existing methods and therapeutic agents, newer arenas should be explored upon to bring out new specific and highly efficacious and economic therapies.

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