Irritable bowel syndrome: Challenges ahead

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Irritable bowel syndrome is one of the most commonly encountered chronic gastrointestinal disorders, accounting for more than half of the patients reporting to gastroenterologists with gastrointestinal symptoms, and incidence of it is rising every day. Although it is not a life-threatening illness, it causes distress to those afflicted and a feeling of helplessness and frustration to the physicians attempting to treat it. It is a motility disorder of the gastrointestinal tract, essentially functional in nature with definite psychosomatic basis. The patients present a variety of symptoms of discomfort without organic abnormalities. Its etiology and functional pathology are unknown. Also there is no specific diagnostic procedure to identify it because the underlying pathophysiology remains unknown. Thus, the diagnosis remains dependent on the symptoms cluster and exclusion of the related pathological diseases. Further, there is no single approach to treat it, hence it is treated with a variety of drugs and other therapies without notable enduring success.

MODERN age is appropriately called the age of stress. Scientific advancement and industrialization have made life hectic and hurried. The incidence of stress in modern society is leading to tremendous increase in various stress disorders, such as anxiety, depression, essential hypertension, irritable bowel syndrome, etc.

Irritable bowel syndrome (IBS) is the most common functional gastrointestinal disorder in clinical practice[1]. It is also one of the poorly understood chronic conditions in part because it is not a disease but a syndrome composed of a number of symptoms with similar manifestation, and is treated with a great variety of drugs and other therapies without notable enduring success[2,3]. IBS can be a very distressing combination of intermittent abdominal pain and irregular bowel habits such as alternating diarrhoea and constipation[4]. It is characterized by a variable combination of unexplained chronic or recurrent symptoms attributed to intestine, abdominal pain, disturbed defaecation (urgency, straining, incomplete evacuation, altered stool form and frequency) and bloatedness[5]. In addition, the patient may experience fatigue, depression, anxiety, insomnia, palpitations and other neurological manifestations. The most prevalent symptoms of IBS are – colon spasticity: inevitably painful, often colicky in nature and can occur anywhere in the abdomen, although the iliac fossa is usually the primary site. Pain can be relieved by defaecation though, it can be more severe after eating or at night. Borborygmi, an audible intestinal rumbling, is often associated with increased flatus or distended abdomen. Although IBS can affect a major portion of the population[6], most do not consult a physician for the condition[7] or respond to reassurance and symptomatic therapies. No specific diagnostic procedures identify IBS, because the underlying pathophysiology remains unknown. Thus, the diagnosis remains dependent on symptoms and exclusion of major organic diseases[8,9]. IBS has almost always been incurable and the approach therefore, can only be palliative. Many drugs have been advocated in treatment of IBS, for instance, spasmolytics, bulking and psychotropic agents, and 5-HT receptor antagonists.

Epidemiology

IBS affects about one in ten of the general population and there is a female predominance[10]. In western countries, females outnumber males by the ratio of 2 : 1 and the exact ratio of female to male in USA was 3 : 2 as reported by Choudhary and Truelove[11]. Pimparker[12] found the ratio reversed in India. Female patients report higher levels of a variety of intestinal and sensory symptoms despite similar levels of IBS severity, abdominal pain, psychological symptoms, and illness impact[13]. Further, among the IBS patients, pain-related Manning symptoms are similar in men and women but mucus, incomplete evacuation, distension and scybala are less common in men[14].

Studies in the UK, USA, France, New Zealand and China indicate that IBS is present in 11–14% of adults[15]. The disease especially is common in the age group of 20–50 years and may also occur in children. There is a higher incidence among whites compared to non-whites and among Jews compared non-Jews. IBS significantly impacts on the quality of life. The economic implication is enormous, representing a multi-billion dollar problem in USA, probably 8 billion dollars annually[16,17]. Although it is not fatal, the morbidity is significant, and the quality of life is impaired to a level comparable with that of a patient who has end-stage renal diseases, diabetes mellitus, or depression[18,19].

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Etiology

The fundamental disturbance in the IBS involves bowel motility. Whether this is constitutional or acquired is difficult to decide. The actual causes of hyperactivity in IBS are often obscure, though certain stimuli to which the bowel reacts are recognized. The causes of IBS have confounded physicians for almost two centuries; researchers have just failed to come across a single specific causative agent. However, constitution, heredity, abnormal motility, myoelectric dysfunction, lactose deficiency, food intolerance, drugs, endocrines, hormones, prostaglandins, infections, infestations, environment and stress factors, all have been accused to play some role in etiopathogenesis of the disease.

Constitutional and hereditary factors

There is no clear-cut evidence to show whether the disease is hereditary or constitutional. Levy *et al.*[20] suggested the possibility of a genetic influence in the etiology of IBS, when they noted that a few members belonging to the same family suffered from similar illness. Recently in a study, Morris *et al.*[21] observed that a substantial proportion of the liability for functional bowel disorders might be under genetic control.

Psychological factors

IBS is a functional disorder of the digestive tract. Functional disorder is a term that is widely misused as a synonym for 'imaginary disorder'. Patients with functional disorders are often viewed as hypochondriacs, psychoneurotics, or malingerers. If this categorization were accurate, then such patients would not be the concern of gastroenterologists, but of psychotherapists and psychiatrists. In fact, functional means no more than a disorder of function, which is a normal manifestation of illness. The term is used to describe disorders of function in which the pathophysiology and underlying pathology remain unidentified.

The notion that the IBS is related to or is even caused by the patient's psychological state is as old as the concept of IBS itself. Many studies attest to the fact that anxiety, mental depression and other types of psychological distress are more likely in IBS patients than in those with organic disease[22–24]. In their classic study, Choudhary and Truelove[11] identified psychological factors, which appeared to influence the onset or exacerbation of IBS in over 80% of their 130 cases.

Both anxiety and depression were found in IBS patients. Some authors consider IBS to be an integral part of depression[25–27]. A higher prevalence of state of anxiety found in patients complaining of bowel symptoms could be linked to the presence of chronic ill status. The higher prevalence of trait anxiety and depression in IBS patients could be responsible for an increase in the activity of the autonomic nervous system[6,27,28].

Stressful stimuli have been shown to disrupt upper gastrointestinal motility in a variety of ways, including mean oesophageal peristaltic amplitude[29,30], rate of gastric emptying[31], small bowel transit in IBS[32] and increased upper oesophageal sphincter pressure[33]. In a study, however, Soffer *et al.*[34] observed that the pre-programmed nature of oesophageal peristalsis is not modulated by stress. Psychological stress was found to increase the amplitude of oesophageal contraction in patients[35].

Since the early observations by Almy[36] on the psychological influence on colon dysfunction, an emerging body of research has indicated that emotions significantly affect the colonic response in patients with IBS. Latimer *et al.*[37] observed no net change in colonic response, when they used a stress interview to elicit emotional reactions from IBS patients, he found increased colonic functions in some patients and a decrease in others. Whitehead *et al.*[38] observed that symptoms of psychological distress are unrelated to bowel symptoms that define IBS, but they do influence those who come to the medical clinic for treatment. In patients with diarrhoea as the predominant symptom of IBS, the relationship between events of daily life and bowel activity may appear very specific, but in patients with constipation, however, the relationship between emotional tension and bowel activity may be somewhat harder to define simply because there is no obvious external response to the emotional tension. IBS is also found to be associated with some psychiatric disorder. In a study, Gupta *et al.*[39] have found nineteen per cent of schizophrenic patients met the criteria for IBS. Welgan *et al.*[40] have reported significantly increased colonic motor and myoelectric activity in patients of IBS when angered.

Diet

Fibre-free processed foods have been attributed as the cause of IBS[41]. Specific foods were found to be provoking symptoms of IBS. Luminal spasmogens derived from diets like acid fruits, tomato and salad are said to be capable of producing IBS. In a study, however, Zwetchkenbaum and Burakoff[42] observed that food hypersensitivity does not play any role in manifestation of IBS. Fat is also believed to be a possible cause in producing the symptoms, particularly that of pain in IBS. Carbohydrate malabsorption can provoke symptoms in some IBS patients but there is no consistent association between such phenomena and the presence of either jejunal hypersensitivity or dysmotility[43]. Further, fructose–sorbitol malabsorption has been found in a high number of IBS patients and thus, thought to play an etiological role. But in a

study, Nelis *et al.*[44] have found no role of fructose–sorbitol malabsorption in the etiology of IBS.

Infestations

In clinical practices, it is a common observation for a physician to find a good number of patients dating back their onset of the symptoms to an attack of intestinal amoebiasis or dysentery. This suggests the role of infections and infestations in the pathogenesis of IBS. Tvede and Williamson[45] observed *Clostridium difficille* in nine per cent of IBS patients. However, Francis *et al.*[46] observed that *Chlamydia trachomatis*, which causes pelvic inflammatory disease, is not a major problem in IBS. Recently the prevalence of *Blastocystis hominis* in stool of IBS patients is reported by Glacometti *et al.*[47]. *Blastocystis hominis* is a common parasite whose role is in dispute. However, a significant rise in IgG_2 subclass antibody levels to *Blastocystis hominis* has been observed in IBS patients[48] and IgG_2 may trigger visceral hypersensitivity of the intestine. The next culprit in this class is *Helicobacter pylori.* The role of its infection in induction of visceral hypersensitivity in upper gastrointestinal tract is still very controversial. However, Gerards *et al.*[49] observed that *Helicobacter pylori* infection may be involved in triggering visceral hypersensitivity in patients with IBS.

Pathophysiology

Knowledge of the pathophysiology of IBS is derived from studies of gastrointestinal motility and the myoelectric activity that governs motility (Figure 1). Because the small intestine is not as accessible as the colon to manometric and electrical studies, most physiological functions have been accumulated from studying the colon[37,50,51]. It is now well established that abnormal myoelectrical activity produces colonic motor dysfunction in the gut[50,51]. However, it is likely that other organs of the gastrointestinal tract, particularly the small intestine, participate to some degree in pathophysiology of IBS[52,53]. Transit of the meal through the small intestine is shorter in IBS patients with diarrhoea and longer in IBS patients with constipation. Both, the pain and altered bowel habits seen in IBS, can be explained on the basis of altered motility, which in turn, may be a response to emotional states (e.g. anxiety, depression, fear and hostility)[54], to meal (gastrocolic response), to neurohumoral agents, to gastrointestinal hormones (e.g. cholecystokinin, glucagon), to toxins (staphylococcal, choleric) and to intestinal distension. Although, there is a wide variability in symptoms, disorders of colonic motility are the most prominent features in IBS. Disturbances in large bowel motility and abnormal rectal sensation are also predominant in IBS patients[51].

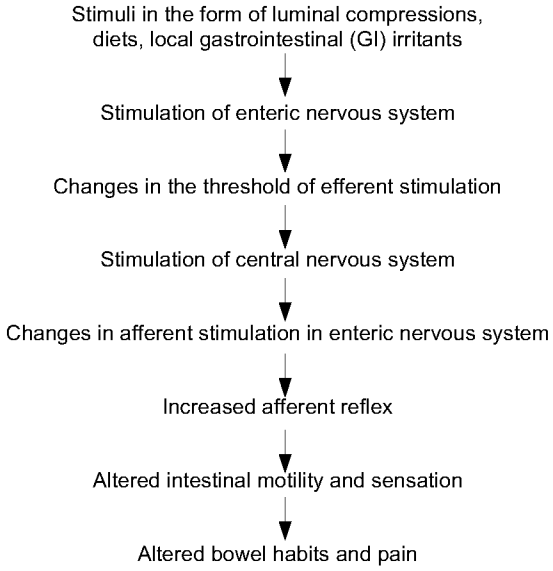

Figure 1. Mechanism of altered gastrointestinal motility in IBS.

IBS occurs when the normal involuntary muscular contractions, which moves bowel contents smoothly through the intestine, become strong and irregular. As the motor activity is controlled by underlying myoelectric activity, it is possible that the abnormal myoelectric activity may set the stage for an abnormal motor response of the end organ, even when neurohumoral stimulation is normal. Smooth muscles electrical activity (myoelectric activity), in the rectosigmoid, in patients with IBS was found increased by several workers[50]. The motor activity of sigmoid colon shows increased motility index in IBS patients with constipation and low motility index with diarrhoea[55]. Disordered oesophageal peristalsis is also reported in patients with IBS[56]. In a study, Smart *et al.*[52] observed prevalent gastrooesophageal reflux in patients with IBS, though the reason why reflux should be associated with the IBS is obscure.

Acute psychological stress can alter the pattern of the migrating motor complex, a pattern of small intestine motility, which is characteristic of fasting and is partly under the control of the central nervous system[57]. In patients with IBS, such stress produces a pattern of 'clustered contractions', which is also found in partial intestinal obstruction. Radiographic studies indicating altered small intestinal transit in patients with IBS, support the notion that small intestinal motility is abnormal[58]. Narducci *et al.*[54] observed increased colonic motor activity during exposure to a stressful situation.

Visceral hypersensitivity is a key factor in pathophysiology of IBS. Studies in experimental animals suggest that stress-induced visceral hypersensitivity is certainly mediated by endogenous corticotropin-releasing factor (CRF) and involvement of structure of emotional motor functions[59]. Other bio-mediators are also associated with

gut and brain in IBS. Intestinal masts cell activation, which results from previous infection and/or intestinal allergy, may play a central role in gut hypersensitivity in both, motor response and visceral perception in IBS[59]. This occurs through mediators acting on the enteric nervous system and smooth muscle cells. Psychological stress may trigger this sensitive alarm system via brain-gut axis[60]. Research into the mechanism of IBS now shifts from a seemingly futile attempt to demonstrate motility abnormality characteristics of IBS, to how events in the gut are handled in the enteric nervous system and perceived in the brain.

Diagnosis

IBS is the symptom complex, which is frequently misdiagnosed and poorly understood. IBS commonly presents with oesophageal symptoms[61] and is associated with abnormal gastrointestinal functions including oesophageal dysmotility[62], abnormal small bowel motility[41,63] and abnormal colonic motility and myoelectric activity[64]. Although there is a wide variability in symptoms, disorder of colonic motility is the most prominent feature in IBS. Disturbance in large bowel motility and abnormal rectal sensation is also predominant in IBS patients[50]. A positive diagnosis is critical to successful management and relies on symptom patterns rather than exhaustive exclusion of other disorders.

The criteria of Manning and colleagues[8] – relief of abdominal pain with defaecation, looser or more frequent bowel movements with pain onset, distension, passage of mucus, and sensation of incomplete evacuation – have been validated and are specific although, not highly sensitive. An international working panel[9] critically reviewed the literature and formulated a definition of IBS by symptoms. They presented their conclusion at a congress in Rome. The Rome criteria for IBS are continuous or recurrent symptoms of; (1) Abdominal pain relieved by defaecation or associated with change in frequency or consistency of stool, and/or, (2) Disturbed defaecation at least 25% of the time: 3 or more of (a) altered stool frequency, (b) altered stool form (hard/loose or watery), (c) altered stool passage [straining, urgency or tenesmus (a feeling of incomplete emptying of the bowels after defaecations)], (d) passage of mucus, (e) abdominal distension.

These criteria exclude two other types of functional disorders, (1) chronic painless constipation and (2) chronic painless diarrhoea that have often been included within the diagnosis of IBS. It also excludes 'functional abdominal pain', which normally means chronic abdominal pain not associated with ingestion of food or with defaecation.

Effective history taking is the key to the diagnosis of IBS. Upper abdominal symptoms though frequently described, are not diagnostically helpful and the emerging notions of 'irritable oesophagus', non-ulcer dyspepsia, and functional biliary pain have narrowed the sites of classic IBS symptoms to the small intestine and colon. Past physical and sexual abuse has been strongly associated with functional bowel disease in women[65], although the role of such events in symptom expression remains unclear. Psychological factors and stressors though not of value in the diagnostic process[66], influence the decision to seek health care and can be important in planning therapy.

Management

Patients with IBS are treated with a variety of drugs, bulking agents, diets and various non-clinical practices, viz. psychotherapy, hypnotherapy, etc. (Figure 1). This multiplicity for treatment of disease reveals that none is strikingly effective, an observation made daily by clinicians caring for these patients. Out of several studies, not a single study offers convincing evidence that any of therapeutic agents is effective in treating the IBS symptoms complex. Moreover, many IBS therapies have significant side effects, which can be justified only if the treatment is truly efficacious. Therefore, the search for the truly effective and safe drug to control physiological disturbance still continues.

Although it is unclear to what extent IBS symptoms represent a normal perception of abnormal function or an abnormal perception of normal function; many believe that IBS constitutes the clinical expression of an underlying motility disorder, affecting primarily the mid and lower gut[67]. As a consequence, drugs affecting gastrointestinal motility have been widely employed with the aim of correcting the major IBS manifestations, i.e. pain and altered bowel functions. Unfortunately, no single drug has proven to be effective in treating IBS symptoms complex.

Patients with IBS may be classified as psychological reactors, food reactors or mixed reactors. The management approach is tailored to the reactive pattern. Psychological reactors may benefit from anti-depressant therapy, psychotherapy, relaxation training and biofeedback. Eliminating offending food from the diet may provide relief to food reactors. In general, placebos, diet, drugs, psychotherapy, hypnotherapy and behaviour therapies are the factors that contribute to effective management of IBS[68].

Drugs

IBS carries a considerable economic and social impact[16,18], which may in part, be due to inefficient diagnosis and inappropriate treatment choice, leading to continuing patient ill health and absenteeism. Even assuming that

IBS can be diagnosed positively using well-established symptom-based criteria, management difficulties remain. Thus, pharmacological treatment choice is still based on single predominant symptom, and many currently available treatments are ineffective in the long term.

IBS is a frustrating disorder to treat. The heterogeneity of symptoms, the lack of reliable pathophysiological marker of improvement and placebos response rate ranging from 20 to 70% have made the assessment of drug efficacy difficult. Klein[69], in a detailed critique of controlled studies from 1966 through 1988, concluded that no single study offered convincing evidence for any drug regimen in IBS. Several classes of drugs look promising for treatment of IBS and are under evaluation[70]. The major aims of medical therapy in IBS are (a) to ameliorate symptoms (pain, bowel movement abnormalities, bloating) and (b) to improve psychological problems of the patients[71].

Antidepressants. Depressive reactions have been reported to be among the most prevalent psychiatric complaint in IBS patients[72,73]. Different treatment trials of antidepressants have been reported in IBS but none prove its global efficacy. Antidepressants are reported to improve diarrhoea-predominant IBS, perhaps because of their anticholinergic effect, analgesic effect, or relief of coexisting clinical depression. Greenbaum *et al.*[74] observed that desipramine has significantly reduced the IBS symptoms. A study of trimipramine claimed statistical significance in its global efficiency measure but never described the measure itself[75]. Benefits of tricyclic antidepressants have been also noted in IBS patients, especially in diarrhoea-predominant IBS.

Opioids. Opioid peptides – enkephalins, betaendorphins and dynorphins, located in the specific sites of the nervous system, participate in regulation of nervous visceral afference and sensitivity as well as of several visceral motor functions induced by the central nervous system and through the enteroenteric and myenteric reflexes. They bind to mu, delta, and kappa receptor subtypes. Exogenous opioid receptor ligands with different affinity for the opioid receptor subtypes have been effectively used to modify and normalize altered gut functions. The mu receptor agonist morphine, meperidine, congeners diphenoxylate and loperamide were found to be effective in IBS patients[76–78]. Out of these drugs, effective symptom control may be achieved with loperamide or diphenoxylate, if specific dietary factors are not found. Since loperamide does not cross the blood–brain barrier, it is preferable to diphenoxylate or other opioids. These drugs slow gastrointestinal transit via effects on circular and longitudinal muscle as well as increasing luminal water absorption and decreasing secretion[4]. However, randomized trials have only demonstrated a benefit for diarrhoea rather than pain[78], and rebound constipation is a problem. They are most useful as prophylactic agents.

Trimebutine [3,4,5-trimethoxybenzoic acid-2-(dimethylamino)-2-phenylbutyl ester], has equal affinity for mu, kappa and delta receptors and its action on the gastrointestinal tract are mediated via (1) an agonist effect on

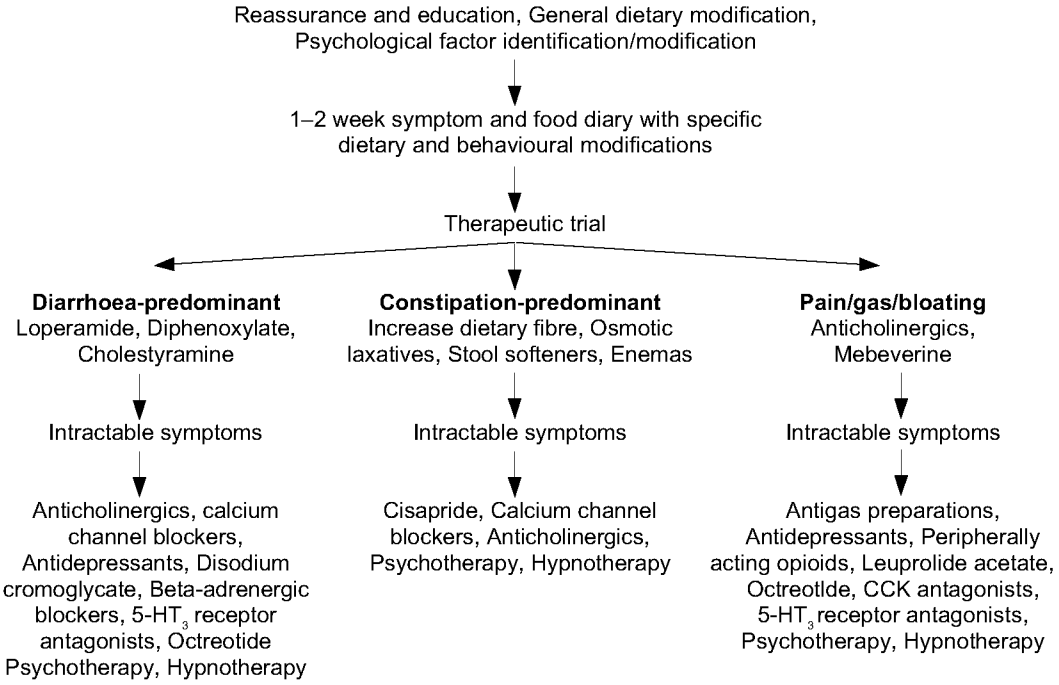

Figure 2. Therapeutic approaches for the irritable bowel syndrome.

peripheral mu, kappa and delta receptors and (2) release of gastrointestinal peptides such as motilin and modulation of release of other peptides, gastrin and glucagon[79]. It accelerates gastric emptying and modulates contractile activity of colon and reduces the abnormal increase in colonic motor activity and accelerates the slow large bowel transit in constipated IBS patients[80]. It is also shown to decrease reflux induced by distension of the gut lumen in animals, and may therefore, modulate visceral hypersensitivity. Clinically it has proved effective in treatment of acute and chronic abdominal pain in patients with IBS. Fedotozine, a kappa agonist, relieves hypersensitivity to colonic distension in IBS patients[81].

Anticholinergic/antispasmodic agents. Their use is based on the pharmacological property of reducing smooth muscle contractility, an implied antispasmodic effect. Among the motor-inhibiting drugs, gut selective muscarinic antagonists (such as zamifenacin and darifenacin), neurokinin-2 antagonist such as (MEN 10627 and MEN 11420) and gastrointestinal selective calcium channel blocker (pinaverium bromide and octylonium), are able to decrease painful contractile activity in the gut (antispasmodic effect) without significantly affecting other body functions[70]. Nicardipine, a calcium channel blocker may be also useful in management of IBS[82]. Cimetropium bromide (antimuscarinic drug) is also found useful in treatment of IBS patients by reducing colonic motor response[83,84].

Novel mechanisms to stimulate gastrointestinal motility and transit includes blockade of cholecystokinin (CCK-A) receptors and stimulation of motility receptors. Loxiglumide (and its dextroisomer, dexloxiglumide) is the only CCK-A receptor antagonist that is being clinically evaluated for treatment of IBS[70]. This drug accelerates gastric emptying and colonic transit, thereby increasing the number of bowel movements in patients with chronic constipation. It is also able to reduce visceral perception. In a recent study, Houghton *et al.*[85] observed that zamifenacin, a potent gut M3 selective muscarinic antagonist, reduces colonic motor activity in patients with IBS.

5-HT antagonists. The discovery of multiple subtypes of serotonin 5-HT (5-hydroxytryptamine) receptors has generated enormous interest over the past few years[86]. 5-HT receptors have been classified into 5-HT_1, 5-HT_2, 5-HT_3 and 5-HT_4 subtypes on the basis of their pharmacological and physiological responses[87,88]. Recently, 5-HT_3 receptor has attracted considerable alternation and our understanding of this receptor has increased dramatically over the past few years because of the discovery and widespread availability of potent and selective antagonists. The 5-HT_3 receptor, when stimulated, results in rapid depolarization of myenteric neurons releasing acetylcholine and inducing fast excitatory postsynaptic potentials[89]. However, the effects are complex because experimental activation of 5-HT_3 receptor can result in release of excitatory and inhibitory gut neurotransmitters, resulting in smooth muscle contraction or relaxation[90]. Mucosal stimulation (e.g. after a meal) stimulates the enterochromaffin cells to release serotonin, which then activates 5-HT_3 receptors in the submucosal plexus as well as in the myenteric plexus and longitudinal muscle[3]. Blocking 5-HT_3 receptors is of clinical relevance in chronic diarrhoea as this leads to reduced contractility, slows colonic transit, and increases fluid absorption[91].

Alosetron (lotronex) is a highly potent and selective 5-HT_3-receptor antagonist. In clinical trials, in patients with IBS, alosetron 1 mg twice daily was found effective in relieving abdominal pain and discomfort. It is found most effective in female patients and particularly in those with diarrhoea predominant IBS[92]. It increases the compliance of the colon to distension and delayed colonic transit in IBS patients[93]. Hence, its most common adverse event is constipation. In *in vitro* studies, it blocks the fast 5-HT_3-mediated depolarization of guinea pig myenteric and submucosal neurons[94]. In a study, Delvaux *et al.*[81] observed that in comparison to placebo, alosetron increased the colonic compliance leading to an increase in the volume required to elicit the first sensation of abdominal discomfort. Alosetron was shown to dose-dependently inhibit the 5-HT-induced skin flare response, increase colonic transit time, increase basal jejunal water and electrolyte absorption, in healthy volunteers[95]. Quinoline derivatives, ondansetron, 5-HT_3-receptor antagonist have also been found effective in patients with IBS[96]. 5-HT_3 antagonists, through suppression of visual afferent functions, may offer a novel approach to visual pain control. Although a preliminary study of ondansetron, a 5-HT_3 antagonist in diarrhoea-predominant IBS suggested improvement in the frequency of loose stools and transit time, relief of abdominal pain was variable[97,98].

Some 5-HT_4 receptor agonists are also being used to treat IBS. These receptors mediate the localized release of neurotransmitters in the colon *in vitro*, including acetylcholine, substance P, vasoactive intestinal peptide and calcitonin-gene-related peptides that stimulates the peristaltic reflux[99]. 5-HT_4 receptors mediate both relaxation and contraction of circular smooth-muscle strips, and hence variable effects on longitudinal smooth muscle; 5-HT_4 activation also induces small bowel and to a lesser extent colonic fluid serotonin[100].

Cisapride (Propulsid) a 5-HT_4 receptor agonist and 5-HT_3 receptor antagonist, enhance motility in the gastrointestinal tract but does not appear to have appreciable prokinetic actions on the colon. It accelerates gastric emptying and enhances gastric accommodation, but has little colonic action in humans[91]. It has been essentially withdrawn from use because of concerns about cardiac toxicity. Norcisapride, a metabolite of cisapride, was in clinical trial but is likely to have little distal gut action.

Tegaserod, a partial 5-HT_4-receptor agonist with high potency and specificity, facilitates about acceleration of proximal colonic transit[101]. Prucalopride, a benzofurancarboxamide, is a selective and potent 5-HT_4-receptor agonist that has been tested in idiopathic chronic constipation[102]. It induces high-propagated amplitude contractions in the colon in a dose-dependent manner in laboratory animals, and in a dose-dependent manner accelerated proximal colonic transit as well as increased stool frequency in healthy volunteers[102]. Recently, a new 5-HT_4 receptor antagonist, SB-207266-A, is found quite worthy for rectal sensitivity and small bowel transit[103].

5-HT_{2b} receptor antagonists have been developed, which may relax longitudinal smooth muscles in the small bowel[104]. 5-HT_6 and 5-HT_7 antagonists have also been synthesized; 5-HT_7 receptors may mediate an inhibitory action on colonic smooth muscle[105].

Bulking agents

Food intake plays a key role in triggering symptoms in patients with IBS. The most important benefit of high fibre diet was observed in IBS patients having hard stool, constipation and urgency[106]. It has been observed that ispaghula, a high fibre diet is quite useful in constipated patients. Various workers observed that bulking agent, e.g. bran, etc., had to do with only constipation; abdominal pain and bloating were not improved[107]. Thus, although there is some evidence that bulking agents may be effective in treating the constipation associated with IBS, there is little reason to believe that they are effective for the entire IBS symptom complex.

Psychotherapy and behavioural techniques

The influence of psychosocial factors on IBS symptoms and limited efficacy to conventional medical therapies for this disorder has led to investigation of the role of behavioural and psychotherapeutic techniques in moderate to severe IBS[108]. The first controlled study of the effects of psychotherapy was reported by Svedlund *et al.*[109]. They found improvements in both somatic and psychological symptoms. Psychotherapy may be helpful for motivated patients, especially if bowel symptoms are of short duration, abdominal pain is not constant and there are overt signs of anxiety or depression. Relaxation training, meditation, stress management procedure, and hypnosis produce sustained reduction in somatic symptoms.

Hypnotherapy

Hypnotherapy is a recent addition to the various approaches in the management of IBS. Patients receiving hypnotherapy showed significantly greater reduction in abdominal pain, abdominal distension and altered bowel habits by the end of treatment compared with controls[110]. Galovski and Blanchard[111] had also observed that the individual symptoms of abdominal pain, constipation and flatulence improved significantly after hypnotherapy. They had also observed a decrease in state and trait anxiety scores. The symptomatic improvement in IBS after hypnotherapy may in part be due to change in visceral sensitivity[112].

Conclusion

In spite of significant advancement in various aspects of IBS, knowledge regarding its etiology, pathophysiology and therapeutics is lacking. There is no single study that offers convincing evidence for single drug therapy. In fact, this disease has become a challenging puzzle for physicians, pathologists and researchers. Continued research is recommended for the search of a genetic marker for IBS, studying the manner in which the enteric nervous system communicates with central nervous system, development of newer and efficient therapeutic approaches in discovering to what extent psychotherapy influences the enteric and central nervous systems as a method of improving IBS symptoms.

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