

## Irritable Bowel Syndrome — More Than Just Abdominal Pain

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### ABSTRACT

Irritable Bowel Syndrome (IBS) is a common gastrointestinal problem characterised by abdominal discomfort and altered bowel function. Although patients with IBS have no increased mortality, significant morbidity exists. The pathophysiology of IBS, diagnosis and treatment of IBS is constantly evolving. The question for the clinician is often how extensively these patients should be investigated and what treatment modalities exist for the treatment of IBS, as such patients can present in a myriad of ways, occasionally in a bewildering manner. Better understanding of the pathophysiology of IBS has led to a more concise and cost-effective diagnostic approach. Newer and novel therapeutic regimes address the fact that IBS is a biopsychosocial disorder. These include psychological treatment, psychotropic medications and newer drugs that target the serotonin-3 and 4 receptors. There is no diagnostic test that is specific for IBS. Neither is there a “cure” for IBS, which remains a chronic and recurring condition. Treatment for IBS may require multiple modalities and even multiple specialities in the management of patients with severe IBS. However, IBS is far from being an “untreatable” disease, and most patients can return to a satisfactory functional level with proper therapy.

*Keywords:* irritable bowel syndrome, psychological therapy, Rome II criteria, serotonin receptors

### INTRODUCTION

Irritable bowel syndrome (IBS) is characterised by abdominal discomfort associated with altered bowel function. These symptoms occur in the absence of structural and serum biochemical abnormalities. This disorder is highly prevalent and is usually associated with emotional distress, impaired health-related quality of life (HRQL), disability, and high health care costs. Abdominal pain or discomfort is sine qua non of IBS. Abdominal discomfort usually occurs in the left lower quadrant but can occur anywhere in the abdomen. Isolated pain above the umbilicus is rare in pure IBS. However, patients with IBS may have symptoms of gastroesophageal reflux disease, dysphagia and globus sensation.

Extra-intestinal manifestations, such as fibromyalgia, sexual dysfunction, urinary symptoms and certain psychiatric disorders, are also seen in IBS patients. Recent research has helped us better comprehend the pathophysiology, symptomatology, diagnosis and treatment of IBS.

### EPIDEMIOLOGY

The point prevalence worldwide is 10 to 20%. A study of 696 Asians in Singapore reported a prevalence of 2.7%.<sup>1</sup> Another local study reported that 50.4% of 2,384 people consulting a gastroenterologist had a functional rather than an organic disorder.<sup>2</sup> A recent study of a random sample of 3,000 households in Singapore found a 8.6% prevalence of IBS using Rome II criteria. This study showed a higher prevalence of IBS in those less than 50 years of age with more than 6 years of education and living in a landed property (and presumably higher social status).<sup>3</sup>

There were no significant differences in prevalence seen in terms of racial groups, marital status and even gender in this particular study.

However, in many other studies, IBS does seem more prevalent in women, with 2:1 female predominance. Interestingly, when individuals who chose to seek medical care for IBS were reviewed, this ratio increased to 4:1 (female:male).<sup>4</sup> The prevalence of IBS also varies with age. Patients below 45 years of age were more

likely to be diagnosed with IBS than those above 45 years (13.5% vs 9.4%).<sup>5</sup>

The rationale for female predominance of IBS is unknown. It could reflect either sociocultural differences in healthcare-seeking behaviour or true biological differences between the 2 sexes. Interestingly, there is a reversal of this ratio in clinics in India, where there is a significant predominance of males (4:1; male:female), which seems to suggest differences in healthcare-seeking behaviour rather than true phenotypic differences.

IBS can occur in children. In children less than 3 years old, the predominant symptom is diarrhoea, pain-predominant IBS is more common in children over the age of 5. Weight loss may occur in these children as they avoid food to try to prevent the pain. A stressful event like teething, a bout of flu, problems at school or at home can trigger symptoms of IBS.

### IMPACT ON PATIENTS

IBS does not lead to excess mortality. The overall life expectancy of these individuals is as good or better than non-IBS controls. There is no increased risk of inflammatory bowel disease, gastrointestinal or colonic cancers. However, IBS does lead to significant morbidity. These patients have rates of absenteeism from work 3 times that of non-IBS individuals. Absence from school, inability to participate in activities of daily living, modifying one's working hours or even giving up one's occupation are not uncommon.

Health-related quality of life (HRQL) addresses the psychological and social consequences of having IBS. Two recent studies using a standard QOL instrument (standard form -36 or SF -36) compared IBS patients with patients with other chronic medical conditions. IBS patients had significantly lower QOL than normal individuals, and poorer scores even when compared to patients with rheumatoid arthritis, diabetes, asthma and gastroesophageal reflux disease.<sup>6,7</sup>

### ECONOMIC IMPACT

It is impossible to fully comprehend a chronic illness without capturing the true cost of IBS on society. The economic impact involves direct costs (for example, medical, hospitalisation), indirect costs (for example, loss of productivity) and the intangible costs of human suffering. There is no available local data, but if one explores the US model, the financial impact is between US\$20 to 30 billion per year (US\$8 billion direct and US\$20 billion indirect costs). Patients with IBS are 3

times more likely to receive a hysterectomy, and have more surgical procedures such as appendectomies.

### PATHOPHYSIOLOGY

The cause of IBS is unknown. However, the symptoms of IBS can be explained physiologically. Three interrelated factors — altered gut reactivity (motility, secretion) in response to luminal (for example, meals, inflammation, bacteria) or environmental stimuli (psychosocial stress); a hypersensitive gut with enhanced pain perception; and altered brain-gut axis, with a greater reactivity to stress and modified pain perception — produce the symptoms experienced by IBS sufferers.

IBS patients have pain at lower volumes and pressures when a balloon is inflated in the bowel, as compared to normal controls.<sup>8,9</sup> A subset of IBS patients associate the development of IBS symptoms with the onset of gastroenteritis.<sup>10</sup> Risk factors for the development of post-gastroenteritis IBS include female gender, duration of the acute diarrhoeal illness, and the presence of significant life stressors occurring around the time of infection. Inflammation can lead to persistent changes in the gastrointestinal nerve and smooth muscle function, resulting in dysmotility, hypersensitivity and gastrointestinal dysfunction. Upregulation of inducible nitric oxide synthase (iNOS), which produces nitric oxide has been seen in inflammatory processes and in IBS patients.<sup>11</sup>

Nitric oxide may have a direct effect on intestinal nerves resulting in disordered motor function and changes in intestinal permeability.

Psychosocial factors play a significant role in worsening symptoms in IBS individuals. It is an accepted fact that psychological stress exacerbates gastrointestinal symptoms.<sup>12</sup> In IBS patients, stress is strongly associated with symptom onset and symptom severity. A large proportion of patients with IBS and other functional bowel disorders have concurrent psychological disturbances — 40 to 90% of patients with functional bowel disorders in tertiary care centres have a psychiatric disorder. Psychological and sociocultural factors can affect the illness experience and treatment outcome of IBS patients. These factors include a history of emotional, or physical abuse, stressful life events, chronic social stress or anxiety disorder and a maladaptive coping style.<sup>13</sup>

There has been a recent surge of interest in the role of serotonergic (5-HT) receptors in the pathogenesis of irritable bowel syndrome. Seven types of serotonin

Table 1. Rome II diagnostic criteria for irritable bowel syndrome

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At least 12 weeks, which need not be consecutive, in the preceding 12 months of abdominal discomfort or pain that has 2 of 3 features.

1. Relieved with defecation; and/or
2. Onset associated with a change in frequency of stool; and/or
3. Onset associated with a change in form (appearance) of stool.

Symptoms that cumulatively support the diagnosis of IBS

1. Abnormal stool frequency (for research purposes, “abnormal” may be defined as greater than 3 bowel movements per day and less than 3 bowel movements per week);
2. Abnormal stool form (lumpy/hard or loose/watery stool);
3. Abnormal stool passage (straining, urgency, or feeling of incomplete evacuation);
4. Passage of mucus;
5. Bloating or feeling of abdominal distention.

The diagnosis of a functional bowel disorder always presumes the absence of a structural or biochemical explanation for the symptoms.

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Table 2. Three-step approach for diagnosis of IBS.

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Step 1	Determine whether the patient satisfies Rome II criteria at first encounter. Rome II criteria is both sensitive and specific for the diagnosis of IBS.
Step 2	Take a detailed history and physical examination to look for the presence of “alarm features”. These include haematochezia, weight loss of more than 3 kg, family history of colon cancer or inflammatory bowel disease, abnormal blood tests (anaemia, electrolyte imbalance), abnormal physical findings (for example, abdominal masses), recurring fever and chronic severe diarrhoea.
Step 3	Perform diagnostic testing.

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receptors have been recognised and these have been named serotonin 1 to 7 receptors.<sup>14</sup> Serotonin 1-4 receptors are expressed in the gastrointestinal tract and are involved in many gastrointestinal functions. Of particular interest are serotonin 3 and 4 receptors which have been shown to regulate motor, sensory and secretory gut responses to intraluminal stimuli.

Stimulation of the serotonin-3 and serotonin-4 receptors have been shown to increase gastrointestinal secretion and the peristaltic reflex, leading to a net prokinetic effect. Drugs like alosetron (serotonin-3 receptor antagonist) and tegaserod (serotonin-4 receptor agonist) have been used to treat diarrhoea-predominant IBS and constipation-predominant IBS respectively.

## DIAGNOSIS OF IBS

IBS should not be considered a diagnosis of “exclusion”, rather a diagnosis of “inclusion”. Therefore, a diagnosis of IBS would entail identifying positive symptoms (for example, Rome II criteria) and excluding other conditions with similar clinical presentations in a cost-effective manner (Table 1).

I adopt a 3-step approach to diagnose IBS, as there are no biochemical or structural tests for this condition (Table 2).

I would recommend diagnostic testing when there is short symptom duration or worsening of symptoms; the patient is above 50 years of age; there is presence of “alarm features”; and there are no concurrent psychosocial difficulties. These tests would include a full blood count, serum electrolytes, erythrocyte sedimentation rate (ESR), serum albumin level, stool ova, cyst and parasites, stool culture and thyroid function tests. More specific tests include stool for fat (for screening of malabsorption) and anti-gliadin and anti-endomysial antibodies for celiac disease (only in patients of Caucasian origin). Stool for occult blood and a colonoscopy should be performed in patients above 50 years of age or in younger patients if there is a positive family history. A plain abdominal X-ray is useful in patients presenting with acute abdominal pain, where an “acute abdomen” (for example, intestinal obstruction) needs to be excluded. Occasionally, a gastroscopy, small bowel series and CT abdomen would be done.

However, it must be emphasised that excessive testing in a patient with obvious IBS is not necessary and may be harmful, as it may reinforce the inherent fears that already exist in the patient. In many cases, a therapeutic trial can be undertaken before further diagnostic testing is performed. This would involve prescribing drugs specific to the patient’s symptoms, and reviewing the

individual 2 to 4 weeks later. A therapeutic trial should only be undertaken if the patient fits the correct demographic profile (for example, young, female) and satisfies Rome II criteria in the absence of “alarm features”.

It should be appreciated that patients with IBS have associated upper gastrointestinal symptoms. These symptoms like upper abdominal pain, bloating, nausea, early satiety and loss of appetite are more apparent in constipation-predominant IBS (C-IBS) patients. Bloating is substantially more common in C-IBS patients (75%) than in D-IBS (41%).<sup>15</sup>

Prolonged distal colonic distention has been shown to retard transit both through the upper GI tract and from the proximal to distal colon. Another potential mechanism linked to dyspepsia is impaired fundic relaxation which in turn is associated with early satiety. Therefore, serotonin-4 receptor agonists like tegaserod, which can cause fundic relaxation, may be useful in such patients.

## TREATMENT OF IBS

The treatment strategy varies according to the nature and severity of the symptoms, the degree of functional impairment and presence of psychosocial difficulties. More often than not, all some patients require are some simple tests, reassurance and symptomatic relief. However, a small proportion of patients with severe and refractory symptoms will require treatment at a tertiary centre with anti-depressants and psychological treatment and support.

### *General Treatment Approach*

This component of therapy is essential to the success of the entire therapeutic regime. A good physician-patient relationship is crucial. The physician has to listen to the patient's concerns, provide a thorough explanation of the disorder, and identify the patient's concerns and expectations. But most of all, he has to set consistent and realistic targets, involve the patient in the treatment and ultimately form a long-lasting relationship with the patient as this is a chronic ailment.

One has to determine the reasons for the patient's visit. These may include environmental stressors (for example, financial or relationship problems, meeting deadlines), new exacerbating factors (for example, food or new medication), personal concern about serious illness (for example, recent family death) and psychiatric co-morbidity (for example, depression, anxiety). Major life events (for example, family death,

marriage), impairment of daily function and a “hidden agenda” (for example, pending litigation) may also initiate a medical consult.

Educating the patient on his condition is of paramount importance as it helps him cope with the illness. Reassurance alone is inadequate, and it should only follow an adequate and conservative diagnostic evaluation. Dietary modification may be useful in some patients, but an overly restrictive diet should be avoided. Substances like fatty foods, beans, nuts, gas-producing foods, caffeine, alcohol and lactose in lactase-deficient patients may aggravate symptoms. Symptom monitoring using a diary can be helpful. It helps to identify certain precipitating factors (for example, food, emotional stressors) and allows the patient to participate in his/her care.

There are specific quality of life instruments like the IBS-QOL or IBS-36 questionnaires, which can be used to objectively assess an IBS patient's response to specific treatments.<sup>16</sup> These are largely research tools and have limited use in normal clinical practice. Patient symptom diaries, on the other hand, can provide useful practical information and chart a patient's progress on treatment.

### *Symptom-Targeted Treatment*

IBS can be divided into constipation-predominant IBS (C-IBS), diarrhoea-predominant IBS (D-IBS) and patients with alternating constipation and diarrhoea. This division is artificial and is done more for ease of choosing the appropriate medication for the patient at a particular time. This is because symptoms tend to fluctuate over time in the same patient, and what may be appropriate now may aggravate his condition at a later date.

Antispasmodics can be used to treat abdominal pain in IBS patients. These include intestinal smooth muscle relaxants (for example, mebeverine, pinaverine) and those with anticholinergic or antimuscarinic properties (for example, dicyclomine, hyoscyamine).<sup>17</sup> However, side effects include visual disturbances, urinary retention, constipation and dry mouth (atropine-like side effects).

Diarrhoea can be relieved by antidiarrhoeals like loperamide or diphenoxylate. Cholestyramine may be considered for a subgroup of patients with a previous cholecystectomy and diarrhoea-predominant IBS.<sup>18</sup> For constipation, increasing dietary fibre (25g/day) may be all that is necessary. Bulking agents like psyllium, wheatbran, corn fibre and calcium polycarbophil can

also relieve constipation. However, bulking agents tend to exacerbate bloating in some patients.

### ***New Drugs***

Two new drugs alosetron (serotonin-3-receptor antagonist) and tegaserod (serotonin-4-receptor agonist) have come into the market for the treatment of IBS.

Serotonin-3-receptors and serotonin-4-receptors are located on the enteric nervous system sensory neurons. Serotonin is released by the gastrointestinal enteroendocrine cells and stimulates peristalsis by binding to the serotonin-3 and serotonin-4 receptors on the enteric nerves.

Alosetron, which is a serotonin-3-receptor antagonist, reduces colonic transit and gastrocolic reflex, thereby reducing diarrhoea and urgency. Two large, randomised, double-blind, placebo-controlled trials showed that alosetron was beneficial in women with D-IBS.<sup>19,20</sup> Constipation was a side effect in 25 to 30% of subjects, and 1 in 700 patients had ischaemic colitis. Consequently, alosetron was withdrawn by the manufacturer. As a result of efforts by patient-advocacy groups, the US Food & Drug Administration authorised the re-introduction of alosetron in June 2002 under specific guidelines that require patients to sign a consent form and the physician to sign a certificate. This drug is not available in Singapore.

Tegaserod is a partial agonist of the serotonin-4 receptor, which accelerates gastric emptying and small and large bowel transit. Three large, randomised, double-blind, placebo-controlled trials of tegaserod for C-IBS showed it improved bloating, pain and constipation in women.<sup>21-23</sup> Tegaserod (6mg twice daily) for 3 months showed an improvement in the global symptoms of IBS in 52% of patients in the last month of therapy. There was a therapeutic gain of 20 to 30% over placebo. The side effects were generally mild, namely transient diarrhoea, headache and abdominal pain. Given the drug's cost and modest advantage over placebo, tegaserod should be reserved for female IBS patients with constipation, who fail to respond to laxatives, fibre and antispasmodic agents.

### ***Centrally Targeted (Psychotropic) Medications***

Antidepressants are recommended for moderate to severe symptoms of pain and may be helpful for less severe symptoms. The antidepressants commonly used are tricyclic antidepressants (TCA) (for example, amitriptyline, doxepin), selective serotonin reuptake inhibitors (SSRIs) (for example, fluoxetine, paroxetine,

sertraline) and novel antidepressants (for example, venlafaxine).

The rationale for treatment includes treatment of psychiatric co-morbidity, alteration of gastrointestinal physiology (visceral sensitivity, motility) and reduction of central pain perception.<sup>24</sup> It is essential that before a patient is started on an antidepressant, she understands the rationale for this mode of therapy, otherwise compliance will be a problem. A treatment plan should be negotiated because benefits would only be apparent after 3 to 4 weeks, following initiation of therapy. Initial phone contact to assess the patient's compliance and side effects of the antidepressants would aid in the success of this form of therapy. Occasionally, dose reduction or change of medication may be required.

SSRIs have a low side effect profile and low-dose TCAs are generally safe. The side effects of the TCAs include sedation, constipation and rarely, hypotension in the elderly, while SSRIs can cause diarrhoea.

### ***Psychological Treatment***

Psychological therapy should be undertaken in patients with moderate to severe IBS, who have failed medical treatment and have evidence of psychological factors or stress which aggravate the patient's symptoms.

The referring physician has to communicate the rationale for psychological treatment and the patient must understand it before such therapy can be successful.

Psychological therapy, which includes cognitive-behavioural, dynamic (interpersonal) psychotherapy, hypnosis and stress management/relaxation, has been shown to be effective in reducing abdominal pain and diarrhoea but not constipation.<sup>25</sup> The best results are seen in tertiary centres with trained professionals skilled in these techniques.

The positive predictors of response are awareness that stress worsens symptoms, at least mild anxiety or depression, predominant symptoms of abdominal pain or diarrhoea, abdominal pain which is intermittent, not constant; and symptoms which are of relatively short duration.

The symptoms of IBS tend to overlap those of more sinister diseases like colonic carcinoma. Not uncommonly, a patient with IBS may develop colonic carcinoma. This is not because IBS predisposes one to the development of a malignancy, but it may occur by pure coincidence. Therefore, it is essential that patients with IBS be made aware of certain alarm

features like haematochezia, significant weight loss, recurring fever or severe chronic diarrhoea, and alert their physician.

### *Future Therapies*

IBS is a biopsychosocial disorder where biological, social and psychological components play a role in disease perception, symptom generation and healthcare seeking behaviour. To be truly effective, a physician must address all these issues in treating an IBS patient.

There is an emerging trend towards involving multiple specialists (family physician, gastroenterologist, psychologist, psychiatrist) and multiple modalities of therapy (medical, psychological therapy, antidepressants) in the management of patients with severe IBS. The challenge for the future is finding the optimal combination of treatment modalities, which is also cost-effective.

The other major area of research is in the development of new drug therapies. With increased understanding of neurotransmitters and hormones in modulating gut motility and sensation, new drugs can be developed targeting specific receptors. These include newer type 3 antimuscarinic agents, NK1 and NK3 receptor antagonists, cholecystokinin antagonists, the  $\alpha_2$  adrenergic agonists and 5HT<sub>1</sub> agonist (buspirone).

Finally, probiotics and alternative therapies can be explored. A placebo-controlled 16-week trial of Chinese herbal medication has showed improved symptom scores and global symptoms and reduced IBS-related interference with life.<sup>26</sup> Probiotics have also been shown to alter gut flora and improve symptoms of IBS.

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