

Irritable Bowel Syndrome: Diagnosis and Treatment

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ABSTRACT

Irritable bowel syndrome (IBS) is the most common functional disorder of the gastrointestinal tract.^{1,2,3} As a result of the lack of specific diagnostic testing and absence of circumscribed biology markers of the disease, its diagnosis is based on a myriad of symptoms.¹ The term irritable bowel syndrome was probably first coined in 1944 by Peters and Bergen.⁴ In 1849, Cumming described the clinical manifestations of Irritable Bowel Syndrome.¹

Irritable bowel syndrome is defined on the basis of the recently modified Rome criteria as the presence of at least 12 weeks (not necessarily consecutive) of abdominal discomfort or pain in the preceding 12 months that cannot be explained by structural or biochemical abnormalities, and that has at least two of the following three features: pain relieved with defecation, an onset associated with a change in the frequency of bowel movements (diarrhea or constipation), or an onset associated with a change in form of stool (loose, watery, or pellet-like). The syndrome can be divided into three subcategories according to the Modified Rome criteria II; those with a predominant symptom of diarrhea, constipation, or constipation alternating with diarrhea. There are several criteria for irritable bowel syndrome, one of which is the Manning criteria, applied in many epidemiological and clinical studies to identify irritable bowel syndrome. However, many investigators disagree with this criteria due to a seemingly poor validity in men.⁴ In an attempt to bring order to the specialty, consensus-based approach is adopted by a group of international experts, which led to the development of the Rome criteria for irritable bowel syndrome (Table 1).⁴ Extra-intestinal symptoms, including headache, backache, urinary and gynecologic symptoms, and fatigue, are more common in the constipation-predominant subgroup.^{1,2,6}

Keywords: irritable bowel syndrome - Rome II criteria

Table 1. Criteria for Irritable Bowel Syndrome

Manning Criteria (1978) [*]	Rome II criteria (1999) [†]
<ul style="list-style-type: none"> • Pain relieved by defecation • Looser stools at onset of pain • More frequent bowel movement at onset of pain • Visible abdominal distention • Mucus per rectum • Feeling of incomplete rectal emptying 	<p>Pain or discomfort for 12 weeks or more in the past 12 months associated with two of the following three:</p> <ul style="list-style-type: none"> • Relieved with defecation • Association with a change in frequency of stool • Association with a change in form of stool <p>Symptoms that cumulatively lend support to the diagnosis:</p> <ul style="list-style-type: none"> • Abnormal stool frequency (>3 bowel movements per day or <3 bowel movements per week) • Abnormal stool form (lumpy/hard or loose/watery) • Abnormal stool passage (straining, urgency or feeling of incomplete rectal emptying) • Passage of mucus • Bloating or feeling of abnormal distension

^{*} Various cutoffs were applied in subsequent clinical and epidemiological studies- e.g. more than two symptoms plus abdominal pain.

[†] Alarm features and psychological measures are not part of the criteria.

EPIDEMIOLOGY

Irritable bowel syndrome is a common disorder affecting approximately 15% of the United States population.^{1,2,20} One third seek medical attention from their primary physician, and only 1% of them are referred to a gastroenterologist.^{2,6} This illness is experienced by women three times more often than men^{1,2}, but in India the incident is more common in men.⁷ It is unclear whether this difference truly illustrates the predomination of women or it is due to more women seeking medical treatment.¹ Menstruation is often related to the occurrence of this illness, indicating hormonal influence.¹ Irritable bowel syndrome can happen in all ages,^{2,4} but is more often found in the young age.^{2,4} The elderly are more likely to have diverticular disease.² Studies suggest that those who seek care are more likely to have behavioral and psychiatric problems.^{1,2}

PATHOPHYSIOLOGY

The pathophysiology of irritable bowel syndrome is very complex because it is not an illness in totality. Some aspects which are thought to be related with the pathophysiology of totality are: change in intestinal motility, visceral hypersensitivity, psychosocial factors, neurotransmitter imbalance, infection,^{1,2,3,4,5,6} as well as food intolerance and allergy.^{4,7}

Altered Bowel Motility

A motility disorder is thought to be the basic problem of irritable bowel syndrome. Some studies described patients complaining about a feeling of incomplete rectal

emptying, solid or liquid stools, especially in patients with constipation as a complaint.

1. Colon motility

Recto sigmoid contraction activity is lower in diarrhea-dominant irritable bowel syndrome patients than in control subjects. Myoelectrical colon activity is divided into 2 types: short spike burst (SSB) in a few seconds and long spike burst (LSB) in 30 seconds. Lower frequencies of both LSB and SSB can be found in diarrhea-dominant irritable bowel syndrome. LSB can be increased as well in constipation-dominant irritable bowel syndrome.

2. Rectal motility

Balloon distension in the rectum triggers recurrent rectum contraction in 75% of diarrhea-dominant irritable bowel syndrome patients as well as in 50% of control irritable bowel syndrome patients with predominant constipation (the difference is not significant). The volume needed to stimulate contraction in rectum is increased in constipation-predominant irritable bowel syndrome.

3. Intestinal bowel motility

The complex motor migration disorder of extended contraction was reported in 61% of irritable bowel syndrome patients and 17% in control subjects in a study by Kellow & Philips (1987), but was not supported by the study by Gorard et al (1994). A group of contraction is part of intestinal bowel contraction distributed in 1-minute durations, and is thus also called "minute rhythm". This contraction

was more commonly found in irritable bowel syndrome than in control subjects in the study by Kellow & Philips (1987), but not in the other study (Gorard et al, 1994). A shorter food transit in the intestinal bowel causes reduced nutrient absorption, causing increased gas production, pain and diarrhea.

Visceral Hypersensitivity

Visceral hypersensitivity is said to be the prime component of irritable bowel syndrome.² Balloon distention studies of the recto sigmoid and the ileum have shown that patients with irritable bowel syndrome experience pain and bloating at balloon volumes and pressures that are significantly lower than those that induce pain in control subjects, a phenomenon referred to as visceral hypersensitivity. One possible explanation is that the sensitivity of receptors in the viscus is altered through the recruitment of silent nociceptors in response to ischemia, distention, intra-luminal contents, infection, or psychiatric factors.¹

There may be increased excitability of the neurons in the dorsal horn of the spinal cord, an area rich in neurotransmitters such as catecholamine and serotonin. Centrally, there may be differences in the way the brain modulates afferent signals from the dorsal horn neurons through ascending pathways. Functional magnetic resonance imaging and positron emission tomography of the brain show different levels of activation in the thalamus and the anterior cingulate cortex after balloon distention of the rectum in patients with irritable bowel syndrome, as compared with normal subjects.

Rectal hyperesthesia has been proven in irritable bowel syndrome, and the severity of symptoms is related to the degree of hypersensitivity degree.² In irritable bowel syndrome, there is increased visceral sensation but somatic perception remains normal.² The underlying mechanism for this phenomenon is unclear. Balloon studies in the recto sigmoid and ileum demonstrated that irritable bowel syndrome patients suffered pain with a balloon volume and pressure significantly lower than control. This phenomenon is related to visceral hypersensitivity. One possible explanation is that sensitivity of receptor in viscus is changed by a nociceptor mediator as a response to ischemia, distention, lumen content, infection, or a psychosocial factor.

These findings, although controversial, suggest a primary central defect of visceral pain processing. Some authors have suggested that hyper-vigilance rather than true visceral hypersensitivity may be responsible for the low pain threshold in patients with irritable bowel syndrome.

Psychosocial Factors

Psychological stress can alter motor function in the small bowel and colon, both in normal subjects and in patients with irritable bowel syndrome,¹ but studies of a causal relation between irritable bowel syndrome and physiological distress show conflicting results.¹⁹ A cohort study of young adults in New Zealand showed that irritable bowel syndrome was not significantly related to an overall diagnostic history of psychiatric illness.¹¹ The presence or absence of a history of abuse in childhood (sexual, physical or both) is correlated with the severity of symptoms in patients with irritable bowel syndrome.^{1,2,4} It has even been proposed that experiences early in life may affect the central nervous system and confer a predisposition to a state of hyper-vigilance.¹

Neurotransmitter Imbalance

Recent studies have suggested that neurotransmitters are involved in the pathogenesis of irritable bowel syndrome.^{1,2,4} Five percent of serotonin is located in the central nervous system, and the remaining 95 percent is in the gastrointestinal tract, within enterochromaffin cells, neurons, mast cells, and smooth muscle cells.¹ When released by enterochromaffin cells, serotonin stimulates extrinsic vagal afferent nerve fibers, resulting in such physiological responses as intestinal secretion and the peristaltic reflex and in such symptoms as nausea, vomiting, abdominal pain and bloating. Preliminary evidence suggests that patients with irritable bowel syndrome have increased serotonin levels in the plasma and in recto-sigmoid colon.

Other neurotransmitters that may have an important role in functional gastrointestinal disorders include calcitonin gene-related peptide, acetylcholine, substance P, pituitary adenylate cyclase-activating polypeptide, nitric oxide, and vasoactive intestinal peptide. These neurotransmitters may provide links not only between bowel contractility and visceral sensitivity, but also between the enteric and central nervous systems. Central processing in irritable bowel syndrome is believed to play a strong causal role in the pathophysiology, based on an fMRI Study.²⁰

Infection and Inflammation

There is compelling evidence that inflammation of the enteric mucosa or neural plexuses initiates or contributes to symptoms associated with irritable bowel syndrome. Mucosal inflammatory cytokines may activate peripheral sensitization or hyper-motility. Gwee et al. reported that in patients with infectious enteritis, the presence of hypochondriasis and stressful life events

at the time of the acute infection predicted the subsequent development of irritable bowel syndrome. To date, no single conceptual model can explain all cases of the syndrome.

Inflammation is associated with the production of mediators such as prostaglandin, bradykinins, nerve growth factors, adenosine and 5-hydroxytryptamine. These mediators induce visceral hypersensitivity, exaggerated motor responses, and increased intestinal secretions, which could contribute to episodic diarrhea.⁴

DIAGNOSIS

The diagnosis of irritable bowel syndrome relies on the experience and expertise of the physician, since laboratory, radiology and endoscopies examinations are

not quite useful. An approach based on dominant symptoms in patients is the best method. An algorithm is used to help physicians in evaluating and treating irritable bowel syndrome patients (Figure 1),^{3,5} in order to make the cost of the treatment more effective.² A complete anamnesis, followed by a complete physical examination and laboratory examination including complete blood check, liver function check and thyrothropine check. The diagnosis of irritable bowel syndrome is considered if the patient's symptoms fit the Rome criteria. In most cases, no abnormalities are found during physical examination or laboratory check and there is no organic-structural problem considered as an 'alarm symptom'.

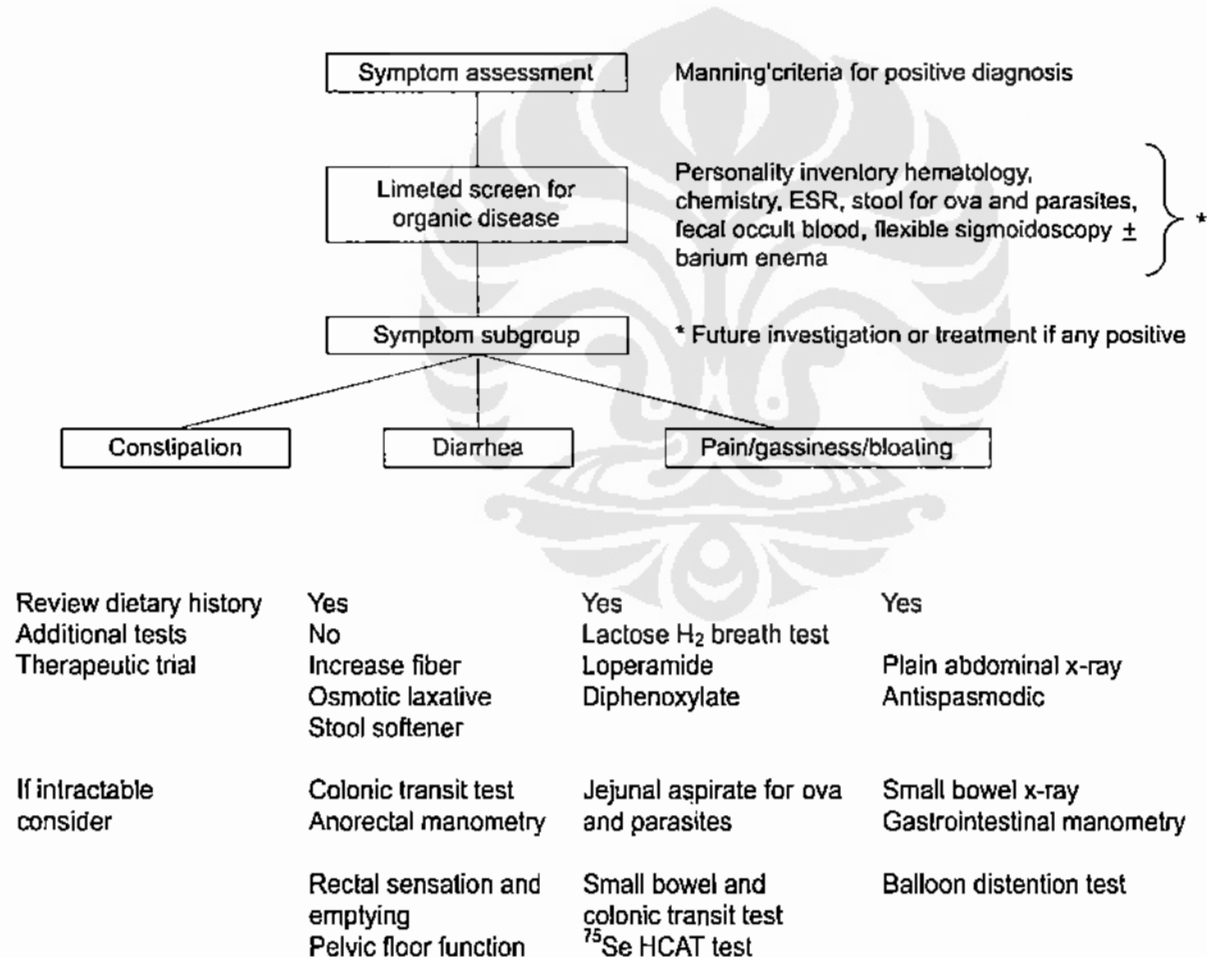


Figure 1. Strategy for Evaluation of Subgroups of Patients with Irritable Bowel Syndrome.

* Note the stepwise series of evaluations guided by the symptom complex (Manning's criteria), by exclusion of organic disease, and by focusing on the major symptom for subsequent testing. ESR=erythrocyte sedimentation rate; 5HT₂=5-hydroxytryptamine; lactose H₂=lactose hydrogen; ⁷⁵Se HCAT=Selenium-75 homocholeic acid taurine.

If there are abnormalities on physical examination or laboratory testing or if there are 'alarm symptoms', irritable bowel syndrome is diagnosed per exclusion after reasonable diagnostic testing has been performed, such as colonoscopy, computed tomography scanning of the abdomen and pelvis, and radiographic evaluation of the small intestines. Alarm symptoms include evidence of gastrointestinal bleeding such as occult blood in the stool, rectal bleeding or anemia; anorexia or weight loss; fever; persistent diarrhea causing dehydration; severe constipation or fecal impaction; a family history of gastrointestinal cancer, inflammatory bowel disease, or celiac sprue; and the onset of symptoms at the age of at least 50 years. In the diagnosis of irritable bowel syndrome, inexpensive noninvasive tests should be used first to rule out other diagnoses.¹⁷ Colonoscopy is indicated when a serious organic disease is reasonably likely and needs to be ruled out.¹⁷

A number of structural or metabolic disorders that are responsive to specific treatment cause symptoms similar to those of irritable bowel syndrome. Lactase

deficiency is a common culprit. Other such disorders include cancer of the colon, diverticulitis, mechanical obstruction of the colon or small intestine, inflammatory bowel disease, enteric infection, ischemia, maldigestion or malabsorption, and endometriosis, suggested by the presence of pelvic pain at the time of the menstrual period. In the absence of alarm symptoms, the presence of one of these structural or metabolic disorders is very unlikely.¹

MANAGEMENT APPROACH³

The aim of therapy in irritable bowel syndrome is to achieve a rapid and sustained relief of troublesome symptoms, to improve the person's long-term quality of life, and to reduce health-care-seeking behavior by empowering the person to take control of the requirements for and timing of therapy.³ The value of a graded multi-component approach to the treatment of irritable bowel syndrome has been emphasized in recent years. One of such approach includes four levels of potential therapy (Figure 2).³

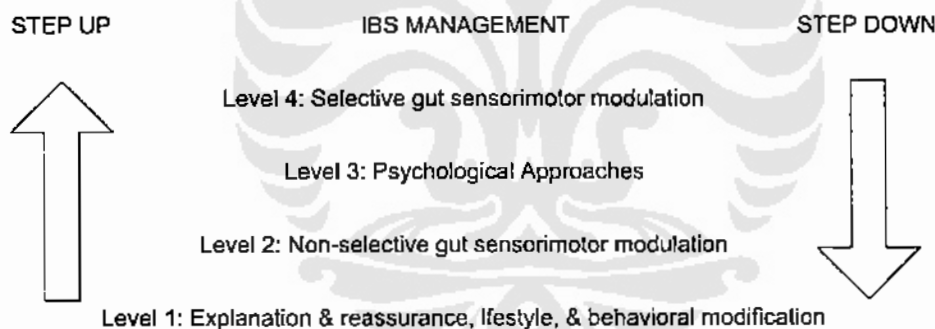


Figure 2. A four Step Approach to The Management of IBS.³

Level 1: Explanation, Reassurance and Modifications of Lifestyle and Behaviors

The reason for the patient's presentation at this time should be addressed. Fear of cancer, recent stressful life events and the like should be explored with appropriate sensitivity. With further questioning, the degree to which the symptoms affect the person's quality of life can be ascertained. Whether the manifestations of irritable bowel syndrome are mild, moderate or severe will affect both the management plan and the extent of continuing consultation. In general, the greater the severity of irritable bowel syndrome, the greater the impairment of quality of life.

Any obvious precipitating factors should be identified. A careful dietary history should be taken. If the person responds that certain foods precipitate symptoms, a food diary may facilitate a more objective identification of recurrent problems. The presence of obvious stressors, such as work or family problems, should be identified, and the relationship of these problems to symptom exacerbations should be sought. Trials of simple relaxation therapy can be undertaken. Therapeutic trials of dietary modification depend on the most prominent symptoms or on the irritable bowel syndrome subgroup. Such trials may include supplementing the diet according to the type of irritable bowel syndrome, with

high fiber, and reduction in intake of lactose, fructose or sorbitol. Reassurance of the patient is vital in the initial management stages. There are four key areas to address. First, the fact that the symptoms and results of investigations positively confirm the diagnosis should be emphasized. Second, that the disorder is a well recognized entity, with a complex pathophysiology that is increasingly defined. Third, despite the most appropriate therapies, residual symptoms are likely to recur or persist from time to time. Fourth, IBS is a diagnosis that does not have serious or structural complications such as diverticular disease. Available data indicate that although patients may remain or again become symptomatic years after a diagnosis of IBS, few develop structural gastrointestinal disorders.

Level 2: Non-selective Gut Sensor Motor Modulation

The choice of therapy at this level depends most on the most dominant symptom.^{2,3} Because symptoms of IBS typically fluctuate, and specific drug treatments are limited, medications should be prescribed as judiciously as required, rather than on a regular basis.³ For cramping abdominal pain, antispasmodics or anticholinergics may be used if the symptoms are moderate or severe. Although controlled clinical trials with these agents have generally been disappointing, meta-analyses do suggest that certain smooth muscle relaxant can be beneficial in some cases.^{1,2,3,4,5} Clinical trials have shown that antidiarrheal drugs are effective for diarrhea, like loperamide.^{1,2,3,4,5} If shown to be helpful initially, this medication can be used effectively on an 'as needed' basis.³

In selected cases, a trial of cholestyramine to control possible bile salt malabsorption may be useful.^{1,2,3,4} For constipation, an increase in dietary fiber and/or fiber supplements should be continued in the longer term once shown to be helpful.^{1,2,3,4} If symptoms continue, a trial of osmotic laxatives such as magnesium-containing salts, lactulose or sorbitol can be tried; these medications are safe for long term use and are often effective.^{1,2,3,4} A recent placebo-controlled 16-week trial of Chinese herbal medicines was reported, and showed that active herbal medicines significantly improved bowel symptoms scores and global symptoms in IBS.^{3,4}

Level 3: Psychosocial Approaches

In moderate to severe IBS, important psychological considerations include a firm identification of; disorders of mood and sleep, of previous psychiatric disease, of previous or current physical or sexual abuse, and of the presence of chronic and highly threatening life stressors. Where the above factors are identified, the role of

psychological treatments should be discussed. The efficacy of psychological treatments has not been well established;^{3,5} the use of these modalities has been considered in detail recently. There is evidence that combining multi component behavioral therapy with medical treatment produces superior improvement in IBS to using medical approaches alone. Low dose tricyclic antidepressants have been used to treat the abdominal pain of IBS. Although selective serotonin re-uptake inhibitors are often used in IBS, randomized controlled trials are lacking.

Level 4: Selective Gut Sensor Motor Modulation

There remains a great need for safe and effective agents to improve the symptom cluster of IBS. These agents should be validated in clinical trials, and targeted at the underlying pathophysiological disturbances in IBS.

Based on recent evidence, the sensory motor disturbances in IBS are related to disturbed serotonergic mechanisms in the gut that act on 5HT₂ and 5HT₄ receptors. Drugs like alosetron, a selective 5HT₂ antagonist, are effective in treating the symptoms of urgency, loose stool consistency and abdominal discomfort in women with diarrhea-predominant IBS.^{15,16} However, this medication is being withdrawn from the market due to the development of severe constipation and the rare occurrence of ischemic colitis.^{15,16}

The 5HT₄ partial agonist tegaserod is well tolerated by patients with constipation-predominant IBS in phase three clinical trials of 16 weeks duration.¹⁴ Reported adverse events were comparable between tegaserod and placebo, with the exception of transient diarrhea in the case of the active drug. The 5HT₄ agonist, prucalopride, has shown similar efficacy in phase three clinical trials in patients with functional constipation. The clinical availability of more effective agents than previously may change the clinical management paradigm outlined. Thus, by analogy with gastroesophageal reflux disease (GERD), one may need to consider not only 'step-up', but also 'step-down' approaches. The 'step up' approach (minimum initial therapy) would have the advantages of avoiding over-treatment and limiting initial drug costs. The disadvantages would be that patients may continue to experience symptoms, and this may lead to unnecessary investigations. 'Step-down' therapy (higher level initial therapy) could have the advantages of rapid symptom relief, thereby avoiding unnecessary investigations and associated costs. The disadvantages would be potential over-treatment and higher initial drug costs.

For patients in whom the disorder is manifested predominantly as abdominal pain, a variety of

medications have been used, and several new agents are under development. Antispasmodic agents may reduce abdominal pain or bloating through anticholinergic pathways; in refractory cases, nitrates are occasionally useful for direct relaxation of smooth muscles. Side effects like sedation, dry mouth and eyes, and weight gain, limit the use of primary tricyclic amines. Secondary tricyclic amines such as anortriptyline and desipramine may be less likely to have side effects.

Fedotozine, a kappa-opioid agonist, has shown promise as a visceral antinociceptive agent, and other kappa-opioid agonists are being developed. In some patients who have abdominal pain that is refractory to all these therapeutics agents, treatment with classic analgesics such as non-steroidal anti-inflammatory agents (perhaps with an initial trial of a cyclooxygenase-2 inhibitor) or, in extreme cases, opioid analogues may control the pain and improve the quality of life. The addictive potential of opioid analogues makes them the last choice for long-term therapy.² In some refractory cases, a short course of antibiotics may reduce the diarrhea, presumably by altering the intestinal flora. The doses of some commonly used agents are shown in (Table 2).¹ Based on one study, hypnotherapy remains an effective treatment for IBS.¹²

Table 2. Dosage Guidelines for Drugs Commonly Used to Treat Irritable Bowel Syndrome¹

DRUG	DOSE
Anticholinergic agents	
Dicyclomine hydrochlorid	20 mg every 6 hours; can be increased to 40 mg every 6 hours if tolerated
Hyoscyamine sulfate	0.125-0.25 mg sublingually every 4 hours (0.375-mg extended-relief tablet; 1 or 2 tablet every 12 hours)
Antidiarrheal agents	
Loperamide	4 mg/day initially, with a maintenance dose of 4-8 mg/day, in a single or divided dose
Diphenoxylate (2.5 mg) plus atropine sulfat (0.025 mg)	2 tablets 4 times a day
Resin cholestyramine	1 packet (9 g) mixed with fluid and taken once or twice a day
Osmotic laxatives	
Lactulose	10 mg/15 ml of syrup; 15-30 mg/day (usual dose), up to 60 ml/day
Polyethylene glycol solution	17 g dissolved in 240 ml (8 oz) of water, taken daily
Tricyclic compounds	
Amitriptyline	25-75 mg/day
Notriptyline	25-75 mg/day
Desipramine	25-75 mg/day

CONCLUSION

1. Irritable bowel syndrome is the most common functional disorder in gastroenterology.
2. The pathophysiology of irritable bowel syndrome is complex, and includes altered bowel motility, visceral hypersensitivity, neurotransmitter imbalance, psychosocial factors, infection, inflammation, and food intolerance.
3. The diagnosis is based on the experience and clinical expertise of the physician, who could refer to the Manning criteria or Rome II criteria.
4. A symptom-based approach is the most pragmatic and appropriate strategy to assist the clinician to achieve a cost effective method for diagnostic purposes.
5. The management of the disease could be approached in a 'step up' or 'step down' manner according to the physician's judgment, each with its own advantages and disadvantages.

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