

## **IRRITABLE BOWEL SYNDROME**

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## PREVALENCE AND EPIDEMIOLOGY

Irritable bowel syndrome (IBS) is the most common functional gastrointestinal (GI) disorder with worldwide prevalence rates ranging from 9-23%. Functional disorders are conditions where there is an absence of anatomical or biochemical abnormalities on diagnostic tests which could explain symptoms. IBS is a chronic functional bowel disorder characterized by abdominal pain or discomfort and alterations in bowel habits. It is the most common disorder diagnosed by gastroenterologists and accounts for up to 12% of total visits to primary care providers. Gender appears to play an important role in IBS. Two-thirds of individuals with IBS are female with an estimated prevalence in women ranging from 14-24%. Of those who seek healthcare services including tertiary and ambulatory care for IBS and other functional bowel disorders, women lead men by a ratio of 2-2.5:1 while others estimate the rate to be higher at 3-4:1. However, the gender distribution appears to be less than 2:1 among IBS non-patients (individuals with symptoms of IBS but who have not sought health care) in the community. It is not known if this increased female prevalence represents a reporting bias, i.e. if female patients are more willing than men to disclose that they have IBS-related symptoms, or if it represents a biological difference.

Not all individuals with IBS symptoms seek medical care for their symptoms. Based on different epidemiological studies performed in different countries, 20-75% of individuals meeting symptom criteria for IBS will seek medical care for their symptoms at some point in their lives. There are between 2.4 and 3.5 million annual physician visits for IBS in the United States, during which 2.2 million prescriptions are written. The cost to society in terms of direct medical expenses and indirect costs associated with loss of productivity and work absenteeism is considerable. It has been estimated that the total cost of IBS is 30 billion dollars per year which includes 20 billion dollars for indirect costs and 10 billion dollars for direct costs.

## SYMPTOMS OF IBS

**Gastrointestinal (GI) symptoms.** The hallmark symptoms of IBS are chronic abdominal pain and/or discomfort and alterations in bowel habits, such as diarrhea, constipation or alternating diarrhea and constipation. Abdominal pain has been reported as primarily crampy or as a generalized ache with superimposed periods of abdominal cramps, although sharp, dull, gas-like, or nondescript pains are also common. The intensity and location of abdominal pain in IBS are highly variable, even at different times within a single patient. The abdominal pain and/or discomfort experienced by IBS patients is often severe enough to interfere with daily activities. Several factors exacerbate or

reduce the pain of IBS. Many IBS patients report increased symptoms during periods of stress or emotional upset such as job or marital difficulties. Defecation may provide temporary relief from the abdominal pain of IBS, whereas ingestion of food may exacerbate the discomfort in a subset of patients.

Based on bowel habits, patients are commonly subclassified into those having mainly diarrhea, mainly constipation, and those alternating between the two patterns. IBS patients with constipation may experience infrequent bowel movements (<3/week), hard stools, straining, and sensation of incomplete evacuation. IBS patients with primarily diarrhea report frequent bowel movements (>3/day), loose and/or watery stools frequent, and urgency. The prevalence of the difference subgroups based on bowel habits is similar. Other common IBS symptoms include bloating, visible abdominal distension, and mucus in the stool.

Upper gastrointestinal symptoms are commonly reported by IBS patients with 25% to 50% of patients reporting heartburn, early satiety, nausea, abdominal fullness, and bloating. Up to 87% have reported intermittent upper abdominal discomfort or pain (dyspepsia) by approximately 40% of patients.

**Extra-intestinal symptoms and overlap with other common pain syndromes.** Many IBS patients also report extra-intestinal (non-gastrointestinal) symptoms such as fatigue, muscle pain, sleep disturbances, and sexual dysfunction. Up to two-thirds of IBS patients report extra-intestinal symptoms compared to less than 15% of healthy individuals. These extra-intestinal symptoms may be due to IBS co-morbidity with other stress-related syndromes such as fibromyalgia, chronic fatigue syndrome, and interstitial cystitis. Epidemiological studies have confirmed the clinical impression that IBS frequently overlaps with these other conditions in the same patient, suggesting shared pathophysiologic mechanisms.

**Psychological symptoms.** Some IBS patients also have psychological distress symptoms such as anxiety and depression particularly in those with severe symptoms and health care seeking behavior. Somatization, anxiety and depressive disorders are also more commonly seen in IBS patients than in healthy controls. Psychosocial trauma and early adverse life events (e.g., parental separation or physical/verbal/sexual abuse history) may profoundly affect symptom severity, daily function, and health outcome. Although these adverse events such as abuse may be quite prevalent in IBS patients, a significant number have not discussed this with anyone and a smaller number will actually inform their physicians.

## DIAGNOSIS OF IBS

The diagnosis of IBS is based on identifying characteristic symptoms and excluding organic disease. An early confident diagnosis permits tests to be minimized and reassures the patient that there is no lethal disease. There are no physical findings or diagnostic tests that confirm the diagnosis of IBS. Therefore, diagnosis of IBS involves identifying certain symptoms consistent with the disorder and excluding other medical conditions which may have a similar clinical presentation. The symptom-based Rome II diagnostic criteria for IBS (Table 1) emphasize a “positive diagnosis” rather than exhaustive tests to exclude other diseases. A validation study of the Rome criteria after excluding patients with symptoms suggestive of other medical conditions other than IBS (“alarm signs” e.g. bloody stools, weight loss, family history of colon cancer, refractory and severe diarrhea) showed that 100% of individuals who met the diagnosis of IBS based on the Rome criteria truly had IBS rather than an alternative diagnosis. At 2 years follow-up, none of the IBS patients required a change in diagnosis.

Other medical conditions which may present with symptoms similar to those seen in IBS include inflammatory bowel disease, GI infections, lactose intolerance, thyroid disease, microscopic or collagenous colitis and malabsorption syndromes such as celiac sprue (Table 2). A medical history and physical examination, laboratory and GI tests can help to exclude these other diagnoses. These tests include routine blood tests, stool studies for infection, and endoscopic procedures such as upper endoscopy, sigmoidoscopy and colonoscopy. In patients < 50 years of age who meet diagnostic criteria for IBS and have no “alarm signs” suggestive of diseases other than IBS, initial screening tests such as a complete blood count to check for anemia and a chemistry panel can be obtained. Other screening tests to consider are a thyroid test (TSH) and a blood test for celiac sprue. However, further tests and procedures such as a colonoscopy are not generally recommended. Patients ≥ 50 years of age with IBS symptoms should undergo a screening colon examination with either a colonoscopy or flexible sigmoidoscopy and barium enema if these tests have not been done previously, regardless if they have alarm signs (see Figure 1).

In some centers, the presence of bacterial overgrowth is often determined because this condition may cause symptoms similar to those of IBS. It is most commonly diagnosed by a lactulose hydrogen breath test. Two studies from the same research group found that 78% to 84% of patients with IBS had bacterial overgrowth. In patients with evidence of bacterial overgrowth, those treated with an antibiotic such as neomycin had a greater reduction in their GI symptoms compared with placebo. Although these data are intriguing, there are some methodologic limitations in these studies and, therefore, the use of widespread hydrogen breath testing for bacterial overgrowth is still not generally advocated.

## PATHOPHYSIOLOGIC MECHANISMS OF IBS

Although psychological and physiological abnormalities have been described, the overall pathophysiology of IBS is not well understood. Similar to other chronic medical conditions, a multi-component conceptual model of IBS, which involves genetic, physiologic, emotional, cognitive, and behavioral factors, has been formulated (Figure 2). Although all factors are closely interconnected, the importance of individual factors in the generation of IBS symptoms may vary greatly between individuals. Previously, IBS was considered primarily a disorder of altered gut motility. Currently, increased bowel sensitivity (visceral hypersensitivity) and altered brain-gut interactions are felt to play a principal role in the pathophysiology of IBS. Recently, it has been found that genetic and environmental factors are important in IBS but further studies are needed to understand the importance of these factors in the prevalence, symptoms, physiologic responses and response to treatment in IBS.

**Altered intestinal motor function.** Altered intestinal motility has been found in IBS, particularly exaggerated contractions (motor response) in the lower (sigmoid) colon to psychological stress and food intake. These alterations may explain why many IBS patients experience typical IBS symptoms following meals and develop exacerbations during stressful life events. These changes in bowel motility are likely due to alterations in the autonomic nervous system outflow to the intestine.

**Increased gut sensitivity.** There has been compelling evidence that IBS patients have enhanced perception of bowel (visceral) stimuli such as food or distensions of the gut wall. The initial clinical observations that led to the hypothesis that patients with IBS have visceral hypersensitivity included the presence of recurring abdominal pain as a principal symptom, the presence of tenderness during palpation of the sigmoid colon (left lower abdominal area) during physical examination in many patients, and excessive pain often reported by patients during endoscopic examination of the sigmoid colon. Published studies measuring visceral sensitivity suggest that a variety of abnormal sensations or perceptions in relation to bowel stimuli may be more frequent in IBS patients. At least two perceptual alterations can be distinguished, a hypervigilance (increased attention or vigilance) towards expected aversive events arising from the bowel, and hyperalgesia (lowered threshold to pain) which is inducible by sustained painful visceral stimulation. These findings are paralleled by similar findings of target system hypersensitivity in other disorders such as fibromyalgia and myofascial pain disorder. In contrast to their enhanced perception of visceral pain, most IBS patients have normal or even decreased pain sensitivity and tolerance for painful cold and mechanical stimulation of somatic (skin and muscle). However, there is a recent study that has demonstrated increased somatic sensitivity to thermal heat in IBS patients. Patients with IBS who also have co-existing

fibromyalgia have increased somatic sensitivity comparable to patients with fibromyalgia alone.

**Increased stress mediators in IBS.** There is increasing evidence to support the prominent role of stress in the pathophysiology and in the clinical presentation of IBS symptoms. There are few published reports on alterations in stress mediators, such as catecholamines and cortisol to stress or visceral stimulation in IBS. Several studies have reported increased in catecholamines (norepinephrine and epinephrine) and cortisol levels in IBS patients. However, it remains to be determined whether these neuroendocrine alterations play a direct role in gut function and symptom generation.

**Altered brain-gut communication in IBS.** A unifying hypothesis to explain the functional bowel disorders is that they result from a dysregulation of the brain-gut axis. An evolving theory is that normal gastrointestinal function results from an integration of intestinal motor, sensory, autonomic and CNS activity and GI symptoms may relate to dysregulation of these systems. Brain imaging studies such as functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) have been performed in IBS patients to measure brain activation patterns to visceral stimuli. These studies suggest that brain activation responses to visceral stimuli are distinctly different in IBS patients compared to healthy individuals. IBS patients may have different emotional and cognitive processing of sensory information from the gut compared to healthy individuals.

**Post-infectious IBS.** Symptoms suggestive of IBS occur in approximately 7-30% of patients following acute GI infections, often persisting for years following complete resolution of the infection. A large cohort study identified a self-reported history of acute gastroenteritis as a major risk factor for the development of IBS. Reported risk factors for the development of post-infectious IBS include female sex, the duration of the acute diarrheal illness and the presence of sustained psychosocial stressors around the time of infection. Post-infectious IBS is not restricted to a particular organism and has been documented with a variety of bacterial infections (*Salmonella*, *Campylobacter* and *E. coli*) as well as parasitic infection. However, the role of acute viral gastroenteritis in this condition is unknown.

In post-infectious IBS, low grade GI inflammation or immune activation may be a basis for altered motility, and/or nerve and mucosal (lining of bowel) function of the gut in IBS. Recent studies have also shown that in a subset of unselected IBS patients (no documented history of a preceding gut infection), there is evidence of increased inflammatory cells in the colon mucosa. It remains to be determined if altered gut immune function is a general characteristic of IBS patients. The implication of stressful life events in the development of post-infectious IBS suggests a convergence of central (brain) and peripheral

(gut) mechanisms in the clinical presentation of this syndrome.

**Gender differences.** In addition to IBS, many functional GI disorders and other chronic visceral pain disorders (e.g. interstitial cystitis and chronic pelvic pain) and somatic pain disorders (e.g. fibromyalgia, myofascial pain disorder) are more common in women than in men. Increasing evidence suggests that gender differences exist in the symptoms, pathophysiologic responses and response to certain treatments in IBS. Female IBS patients are more likely to be constipated, complain of abdominal distension and certain extra-intestinal symptoms. Studies have also supported an influential role of ovarian hormones (e.g. estrogen and progesterone) on bowel function and pain sensitivity which can in part explain the gender differences in IBS. Several investigators have reported a variation in GI symptoms during different phases of the menstrual cycle, particularly increased abdominal pain and loose stools at the perimenstrual (just prior to and at time of menses) phase.

## TREATMENT

Treatment of IBS includes both non-pharmacologic and pharmacologic therapies. An important component of non-pharmacologic treatment for IBS is a successful physician-patient relationship. The physician should strive to establish effective bi-directional communication with the patient, gain the patient's confidence with a concise, appropriate medical evaluation and offer reassurance and education that IBS is a real medical condition with a potential impact on health related quality of life but without significant long-term health risk. Some IBS patients, especially those presenting with new onset of symptoms, express relief that their symptoms are not caused by a serious condition such as malignancy. Other components of non-pharmacologic treatment of IBS include diet recommendations, lifestyle modifications, and psychosocial intervention if needed.

Patients with mild IBS symptoms comprise the most prevalent group, and are usually treated by primary care practitioners, rather than specialists. These patients have less significant functional impairment or psychological disturbance. These patients do not see a clinician very often, and usually maintain normal daily activities. Treatment is directed toward education, reassurance, and achievement of a healthier lifestyle and occasional medication. Dietary advice may include avoiding offending foods which can trigger symptoms (e.g. lactose or fructose products, fatty foods, caffeine, gas-producing foods). Fiber supplementation has been shown to be effective for symptoms of constipation.

Pharmacologic therapy is best used in IBS patients with moderate to severe symptoms refractory to physician counseling and dietary manipulations. First line treatment has traditionally been aimed at treating the most

bothersome symptom because of the lack of effective treatment for the overall improvement of multiple symptoms in IBS patients. However, new therapies for IBS have been recently introduced and have been shown to effectively treat multiple symptoms of IBS.

**Anticholinergic/Antispasmodic agents.** After fiber preparations, antispasmodic agents are the next most commonly prescribed group of medications for the treatment of IBS. However, several studies do not provide firm evidence that anticholinergic agents are efficacious in the IBS population as a whole. Only a few of these antispasmodics have been shown to be more effective than placebo in relieving abdominal pain in high quality clinical IBS trials but these are not currently available in the U.S.

**Antidiarrheal agents.** In IBS patients with diarrhea, antidiarrheal agents such as loperamide and diphenoxylate can be effective in decreasing bowel movement frequency, improving stool form by enhancing intestinal water and ion absorption, and increasing anal sphincter tone at rest. These physiologic actions seem to explain the improvement in diarrhea, urgency, and fecal soiling observed in patients with IBS. These medications do not typically relieve abdominal pain and may cause constipation.

**Psychotropic medications.** The rationale of using this class of drugs in IBS may relate to several factors, such as the prominent co-morbidity of IBS with psychologic distress symptoms and the effects of these agents on gut motility and pain sensation. Among the classes of antidepressant medications, the tricyclics have been most extensively evaluated in IBS. At lower doses than those usually used to treat depression (starting at 10 mg and up to 75 mg nightly), amitriptyline and desipramine have been found to be significantly more effective than placebo in patients with IBS. Antidepressants have analgesic (pain relief) properties, which may benefit patients independently of the psychotropic effects of the drugs. Treatment with tricyclics should begin with low doses (e.g., 10 mg/day) and increased as needed up to full therapeutic doses. Selective serotonin reuptake inhibitors (SSRIs, e.g. paroxetine, citalopram) and selective serotonin and noradrenergic reuptake inhibitors (SNRIs, e.g. venlafaxine) have not been well studied for treatment of IBS, and are more expensive, but have less side effects than tricyclics and empirically may help reduce painful symptoms and improve general well-being and quality of life.

**Novel serotonin agents.** The prominent role of serotonin in GI motility and sensation has led to the development of novel serotonin agents such as alosetron and tegaserod in the treatment of IBS. Most of serotonin (also known as 5-HT) in the body resides in the bowel wall within enterochromaffin cells lining the gut (mucosa) and nerve cell bodies. Serotonin is released from the enterochromaffin cells and acts on receptors on the nerves within the bowel wall. These nerves may be part of the

nervous system which resides completely within the bowel wall, known as the enteric nervous system, or may be nerves that transmit painful and non-painful information by projecting from the bowel to the spinal cord and brain. Activation of these nerves by serotonin leads to the release of other neurotransmitters and through their actions, it plays a major role in gut motility, secretion and sensation.

Alosetron (Lotronex<sup>®</sup>), which is a 5-HT<sub>3</sub> antagonist, has been shown to be effective in relieving pain, normalizing bowel frequency, and reducing urgency in non-constipated IBS female patients. This medication was approved by the FDA last year but was later withdrawn because of the adverse events of constipation and ischemic colitis, the latter being observed in 0.1%-1% of patients receiving the medication. Future studies are being planned to determine if there is a causal association of alosetron and ischemic colitis. However, alosetron has recently been re-approved and now is available for the treatment of women with severe diarrhea-predominant IBS under the Restricted Use Program. Alosetron is indicated only for women with severe diarrhea-predominant IBS who have: chronic IBS symptoms (generally lasting  $\geq$  6 months), no evidence of anatomic or biochemical abnormalities of the GI tract which could explain their symptoms, and failed to respond to conventional therapy. IBS is considered severe if it includes diarrhea and  $\geq$  1 of the following: frequent and severe abdominal pain/discomfort, frequent bowel urgency or fecal incontinence, or disability or restriction of daily activities due to IBS. Physicians must enroll in the Restricted Use Program in order to prescribe alosetron. Patients should discuss with their physicians about the risks and benefits of the medication before being prescribed it. Both should sign the Patient-Physician Agreement form. The starting dose of alosetron is now 1 mg orally once daily. If the patient does not experience complete relief of their symptoms after 1 month, the dose can be increased to 1 mg orally twice daily which was the originally approved dose. Any patient who experiences increased abdominal pain, blood in their stool and/or constipation should immediately stop their medication and contact their physician.

Tegaserod (Zelnorm<sup>®</sup>) is a partial 5-HT<sub>4</sub> agonist, which has been shown to be effective in relieving the global symptoms of IBS with constipation. It has been recently approved for the treatment of IBS with constipation in women. Tegaserod has been shown to accelerate GI transit time in IBS patients and therefore would increase stool frequency, and increase electrolyte secretion in the bowel and thus improve stool form. In addition to its motility enhancing properties, tegaserod has been shown to have pain inhibitory properties in animal studies and therefore may reduce abdominal pain although human studies are needed to confirm this effect. Unlike other currently available medications for IBS with constipation, tegaserod appears to be effective in treating the multiple symptoms of IBS. The subject's global assessment of relief of IBS symptoms, change in number of bowel movements,

abdominal pain and bloating are all reportedly improved in female patients with IBS with constipation taking tegaserod as compared to placebo. The only adverse events which were seen at a small but significantly higher rate in patients taking tegaserod compared to placebo were headache and transient diarrhea.

**Psychological treatments.** Referral for psychological treatment can be recommended as part of a multi-component treatment program to help the patient better manage the symptoms, or to address psychosocial difficulties (e.g., abuse, loss) that may interfere with daily function and ability to cope with the illness. In general, these treatments are reserved for patients with moderate to severe symptoms, particularly if they experience psychological distress. However, the patient must be motivated and see this type of treatment as relevant to their personal needs. Psychological treatments used to treat IBS include psychotherapy (dynamic and cognitive-behavioral therapy), relaxation therapy, hypnotherapy, and biofeedback therapy. Psychological treatments can also be combined. Review of well-designed treatment studies of IBS supports the superiority of psychological treatment over conventional medical therapy. Follow-up studies (duration 9-40 months), have demonstrated that psychological treatment maintained superiority over placebo, indicating that these methods have lasting value. The choice of treatment will depend on patient requirements, available resources and the experience of the therapist.

## CONCLUSIONS

IBS is a common, chronic disorder characterized by exacerbations and remissions, which presents with symptoms of abdominal pain and/or discomfort and altered bowel habits. It has a chronic relapsing course and can overlap with other functional GI (dyspepsia) and non-GI (fibromyalgia) disorders.

The clinical diagnosis of IBS is based on identifying symptom criteria with a "positive diagnosis" and excluding organic disease with minimal diagnostic evaluation. Clinicians should feel secure with the diagnosis of IBS, if made properly, because it is rarely associated with other explanations for symptoms. Although there are many expensive and sophisticated tests available for the evaluation of IBS symptoms, these are generally not needed for patients with typical symptoms and no features suggestive of organic diseases.

An integrated diagnostic and treatment approach first requires an effective physician-patient relationship. A careful history will also identify the need for diagnostic studies and treatments as determined by the nature and severity of the predominant symptoms, and the degree and extent of influencing psychosocial and other factors.

The fact that definite structural or biochemical abnormalities for these disorders cannot be detected with conventional diagnostic techniques does not rule out the possibility that neurobiological alterations will eventually be identified to explain fully the symptoms of most functional disorders. Examples of such a shift in perspective from symptom-based disorders without detectable abnormalities to medically treatable diseases based on specific neurobiological alterations include affective disorders (depression, anxiety) and migraine headaches. Similar to other chronic illnesses, a multicomponent model that involves physiologic, affective, cognitive, and behavioral factors can be formulated for IBS. Although all factors are closely interconnected, the importance of individual factors in the generation of IBS symptoms may greatly vary between individuals. Physiologic factors implicated in the generation of IBS symptoms include hypersensitivity of the GI tract to normal events, autonomic dysfunction including altered intestinal motility response to stress and food intake, alterations in fluid and electrolyte handling by the bowel, and alterations in sleep.

Many of the traditional therapies have been used to treat specific IBS symptoms because they have not been shown to significantly relieve global symptoms, which would improve an overall sense of well-being. However, the discovery of novel serotonergic agents such as tegaserod and alosetron have been shown to be effective in treating global symptoms in patients with IBS compared with placebo. More recently published studies evaluating the efficacy of antidepressants, such as tricyclics and SSRIs, suggest that these medications may help improve general well-being in addition to treating psychological comorbidity in affected individuals but further studies are needed. Psychological and behavioral therapies have also been shown to be effective for IBS however it potentially can be limited by the availability of experienced therapists. Instituting a multidisciplinary approach using non-pharmacologic and pharmacologic therapeutic modalities may result in the most effective outcome. Future studies will further enhance our understanding of this condition and lead to newer, more effective treatments.

## Recommended Reading:

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### **Resources for Patients and Providers**

**<http://www.uclacns.org>**

**<http://www.uclamindbody.org>**

**<http://iffgd.org>**

Figure 1.

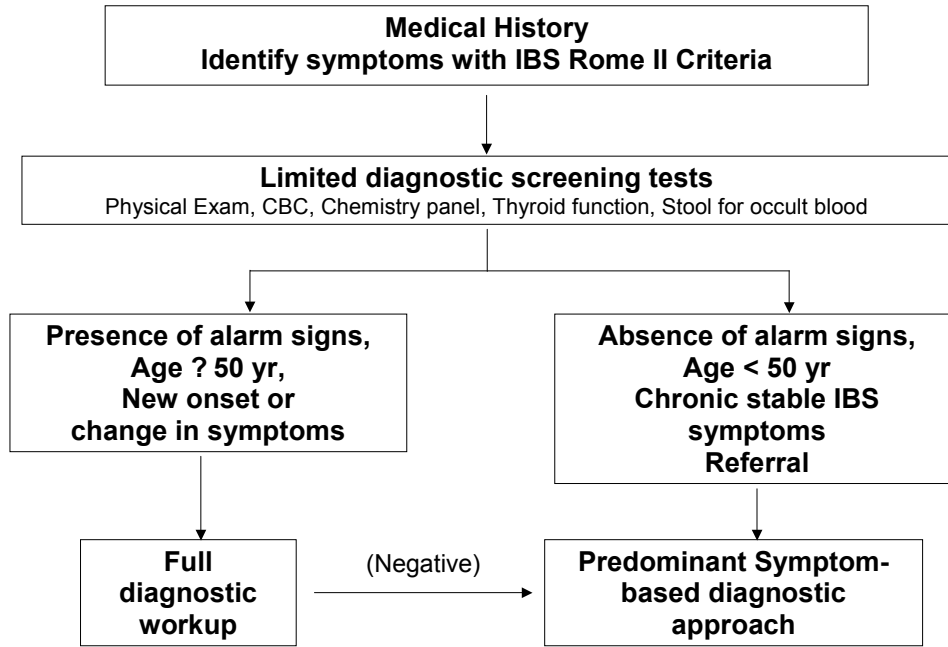


Figure 1. Diagnostic evaluation of IBS patients

Figure 2

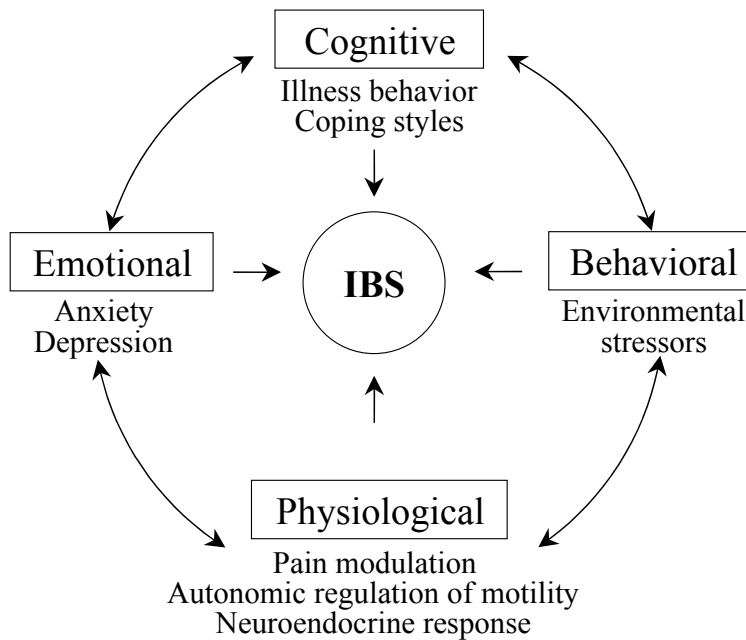


Figure 2. Multicomponent model of irritable bowel syndrome (IBS). Development of IBS symptoms can be explained by the interrelation of cognitive, behavioral, emotional, and physiological components. Mayer EA. Am J Med. 1999;107(5A):12S-19S

**Table 1****ROME II Diagnostic Criteria**

At least 12 weeks, which need not be consecutive, in the preceding 12 months of abdominal discomfort or pain that has two of three 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

**Table 2.****Differential Diagnoses of IBS**

<b>Inflammatory bowel disease</b>
<b>Colorectal carcinoma</b>
<b>Medications</b>
<b>Gastrointestinal infections (e.g., Giardia, Entamoeba histolytica, Yersinia, Strongiloides)</b>
<b>Lactose Intolerance</b>
<b>Endocrine disorders (Hypo or hyperthyroidism, Diabetes)</b>
<b>Medications (e.g., laxatives, magnesium-containing antacids)</b>
<b>Microscopic or collagenous colitis</b>
<b>Bacterial overgrowth</b>
<b>Malabsorption syndromes (e.g., celiac sprue, pancreatic insufficiency)</b>
<b>Chronic intestinal idiopathic pseudoobstruction</b>
<b>Endocrine tumors (e.g., gastrinoma, VIPoma)</b>