Irritable Bowel Syndrome (IBS): Introduction

Irritable Bowel Syndrome (IBS), which is classified as a functional gastrointestinal disorder, is a chronic condition of the lower gastrointestinal tract (Figure 1) that affects as many as 15% of adults in the United States. Not easily characterized by structural abnormalities, infection, or metabolic disturbances, the underlying mechanisms of IBS have for many years remained unclear. Recent research, however, has lead to an increased understanding of IBS. As a result, IBS is now considered an organic and, most likely, neurologic bowel disorder.

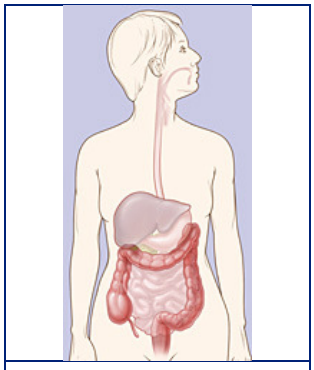

Figure 1. Location of the colon in the body.

IBS is often referred to as spastic, nervous or irritable colon. Its hallmark is abdominal pain or discomfort associated with a change in the consistency and/or frequency of bowel movements. Although the causes of IBS have not to date been fully elucidated, it is believed that symptoms can occur as a result of a combination of factors, including visceral hypersensitivity, altered bowel motility, neurotransmitters imbalance, infection and psychosocial factors (Figure 2).

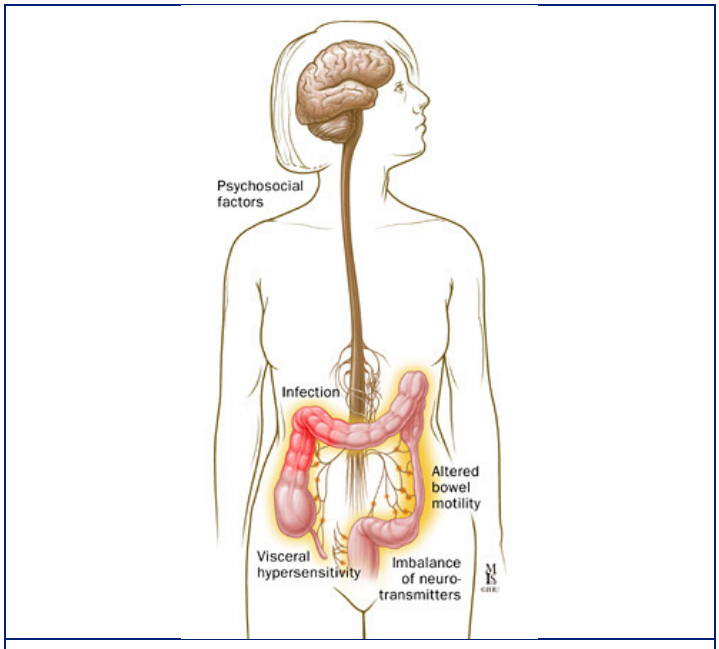

Figure 2. Possible causes of Irritable Bowel Syndrome.

The frequency of IBS in any given population depends, in part, on the ethnic and cultural background of the population being studied, and the criteria used to diagnose the disease. Eight to 20% of adults in the Western world report symptoms consistent with IBS (60-70% of these are women). In the United States, as many as 15% of adults (about 35 million people) report IBS symptoms (note: the frequency of IBS among Caucasian, African American and Hispanic populations is relatively consistent). Asia and Africa have similar rates to those in the United States, and the Western world in general. In India and Sri Lanka, IBS is more common among men, although it is possible that this is a result of differences in symptom reporting and health care use between genders. Physiological differences between men and women impact gastrointestinal transit time, visceral sensitivity, central nervous system processing, and specific effects of estrogen and progesterone on gut function. While the effect of gender on seratonergic agents efficacy has been examined, much less is understood about gender differences in nondrug therapies for treatment of IBS. Overall, the differences in IBS incidence rates between genders and populations can probably be explained by viewing IBS as a biopsychosocial disorder in which not only abnormal sensation and motility, but also psychosocial factors play a role.

Only about 10% of people with symptoms of IBS present to physicians for evaluation or treatment. In spite of this, the health-care related costs of IBS are substantial. IBS accounts for nearly 3.5 million physician visits in the U.S. annually, and is the most common diagnosis in gastroenterologists' practice. In addition, several studies have suggested that the impact of IBS on health-related quality of life is equally as significant as congestive heart failure and dialysis-dependent renal failure. Patients with IBS have higher rates of absenteeism from work and school. In one U.S.-based study, the direct healthcare costs for patients with IBS were estimated at $8 billion, while indirect costs were estimated at $25 billion per year. Such studies overlook the significant societal impact of IBS in terms of physical and emotional function, interpersonal relationships and psychological distress.

What is Irritable Bowel Syndrome?

Irritable Bowel Syndrome is a chronic condition of the lower gastrointestinal tract. The symptoms of IBS may include abdominal pain, distention, bloating, indigestion and various symptoms of defecation. There are three subcategories of IBS, according to the principal symptoms. These are pain associated with diarrhea; pain associated with constipation; and pain and diarrhea alternating with constipation (Figure 3). Each patient's symptoms are unique. While IBS may occur as an occasional nuisance for some people, others may experience intense pain that compromises their quality of life.

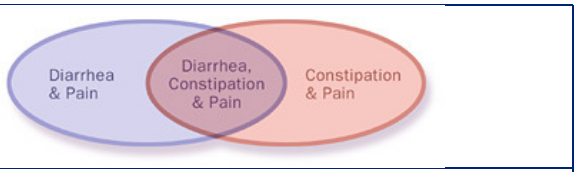

Figure 3. The three symptom subcategories of Irritable Bowel Syndrome.

IBS does not lead to more serious disease, nor does it shorten the life span of those affected. It is not an inflammatory, infectious or malignant condition and has not

been found to lead to colitis. Furthermore, IBS is not a psychiatric disorder, although it is tied to emotional and social stress, which can affect both the onset and severity of symptoms. While IBS is not considered a life-threatening disease, IBS patients suffer from a disproportionately higher rate of co-morbidity with other disorders, such as fibromyalgia, chronic fatigue, pelvic pain and psychiatric disorders.

Primary features of the syndrome include motility, sensation and central nervous system dysfunction. Motility dysfunction may be manifest in muscle spasms; contractions can be very slow or fast. An increased sensitivity to stimuli causes pain and abdominal discomfort. Researchers also suspect that the regulatory conduit between the central and enteric pathway in patients suffering from IBS may be impaired.

Research suggests that many patients with Irritable Bowel Syndrome have disorganized and appreciably more intense colonic contractions than normal controls. A study at Johns Hopkins reported that healthy volunteers had 6–8 peristaltic contractions in the colon in a 24-hour period. In contrast, IBS volunteers in whom the primary symptom was constipation had almost no contractions, and IBS volunteers in whom the primary symptom was diarrhea had as many as 25 contractions a day. Researchers have also found that pain is frequently associated with irregular motor activity of the small intestine when compared with either normal controls or patients with Inflammatory Bowel Disease. Patients with this disease appear to have a defect of visceral pain processing—although whether or not this is a true hypersensitivity or hyper-vigilance remains controversial. Interestingly, however, ileal and rectosigmoid balloon-distention studies have demonstrated that patients with IBS experience pain and bloating at balloon pressures and volumes that are significantly lower than those which cause symptoms in normal controls.

Pathophysiology

The biopsychosocial model of IBS integrates a number of psychosocial, motility, sensory abnormalities and abnormalities in central nervous system processing of visceral pain as the causes of abdominal pain and altered bowel habits (Figure 4.)

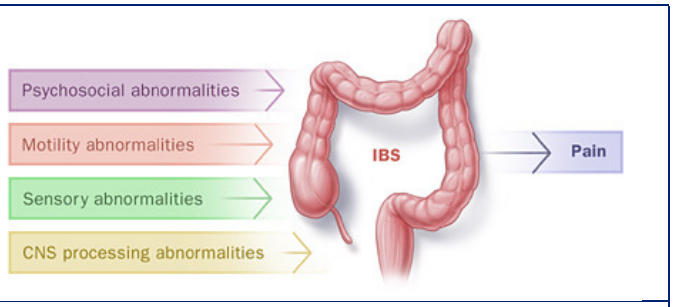

Figure 4. The biopsychosocial model of Irritable Bowel Syndrome.

Motor dysfunction contributes to some symptoms of IBS, such as abdominal pain, defecatory urgency, and postprandial bowel movements. Rapid small bowel and colonic transit times have been reported in patients with diarrhea-predominant IBS. Patients with constipation-predominant IBS may have a component of disordered defecation, resulting, at least in part, from abnormal function of the pelvic floor and anal sphincter muscles. Another factor in motor dysfunction is the abnormal passage and handling of gas.

Colonic and rectal hypersensitivity (also called “visceral hyperalgesia”) are also important factors in the causation of symptoms. Enteric propulsion and sensation are, in part, mediated by acetylcholine and serotonin (5HT).

The physiology of sensation in the gut is multifaceted. Enteroendocrine cells transmit mechanical and chemical messages. The communication between gut and brain results in reflex responses mediated at three levels—prevertebral ganglia, spinal cord and brainstem. 5-HT, substance P, CGRP, norepinephrine, kappa opiate and nitric oxide are all involved in the perception and autonomic response to visceral stimulation (Figure 5). Sensation is conveyed from the viscus to the conscious perception via neurons in vagal and parasympathetic fibers. Afferent nerves in the dorsal root ganglion synapse with neurons in the dorsal horn. These signals result in reflexes that control motor and secretory functions as they synapse with efferent paths in the prevertebral ganglia and spinal cord. Pain is processed through spinal afferents in the dorsal horn. Ultimately, stimulation of the brainstem brings sensation to a conscious level (Figure 6). Bidirectional signaling between the brainstem and the dorsal horn mediate sensation. The descending pathways are primarily adrenergic and serotonergic and affect incoming stimuli. End organ sensitivity, stimulus intensity changes or receptive field size of the dorsal horn neuron and limbic system modulation are the mechanisms involved in visceral hypersensitivity.

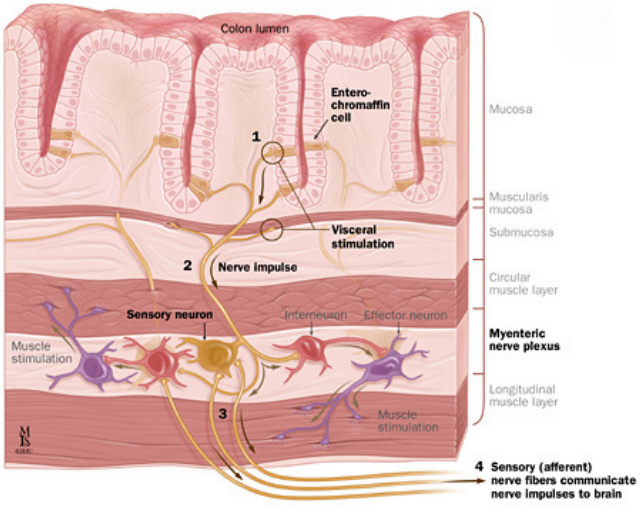

Figure 5. Nerve cell communication in the wall of the colon.

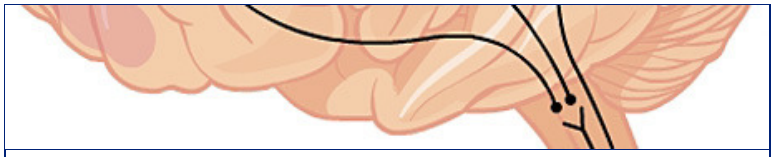

Figure 6. Sensory pathway in Irritable Bowel Syndrome: an animated sequence (To view, click on the image above).

Enteric inflammatory cells may also play an important role in the pathophysiology of Irritable Bowel Syndrome. Clinicians have for many years recognized that the onset of IBS often follows an episode of acute gastroenteritis. Inflammation may alter intestinal cytokine milieu and motility, both of which can result in an increase in a patient's pain sensation. The menstrual cycle may also affect gut sensation and motility. Other factors, such as malabsorption of sugars (lactose, fructose, and sorbitol), probably aggravate underlying IBS, rather than serving as root causes of the disorder. In patients with rapid transit times, short or medium chain fatty acids can reach the right colon and cause diarrhea.

Symptoms

The hallmark of IBS is abdominal pain or discomfort associated with either a change in bowel habits or disordered defecation. The pain or discomfort associated with IBS is often poorly localized and may be migratory and variable. It may occur after a meal, during stress or at the time of menses. In addition to pain and discomfort, altered bowel habits are common, including diarrhea, constipation, and diarrhea alternating with constipation. Patients also complain of bloating or abdominal distension, mucous in the stool, urgency, and a feeling of incomplete evacuation. Some patients describe frequent episodes, whereas others describe long symptom-free periods. Patients with irritable bowel frequently report symptoms of other functional gastrointestinal disorders as well, including chest pain, heartburn, nausea or dyspepsia, difficulty swallowing, or a sensation of a lump in the throat or closing of the throat (Figure 8).

Patients with IBS are generally classified according to the type of bowel habits that accompany pain. Some patients have diarrhea-predominant symptomatology, others constipation-predominant, and still others have a combination of the two. Some patients alternate between different subgroups.

Symptoms may vary from barely noticeable to debilitating, at times within the same patient. In some patients, stress or life crises may be associated with the onset of symptoms, which may then disappear when the stress dissipates. Other patients seem to have random IBS episodes with spontaneous remissions. Still others describe long periods of symptoms and long symptom-free periods.

In general, the symptoms of IBS wax and wane throughout life, but the majority of patients seen by physicians is 20–50 years old. In approximately 50% of patients, symptoms begin before age 35. The disorder is also recognized in children, generally appearing in early adolescence. Many patients can trace the onset of symptoms back to childhood. The prevalence of IBS is slightly lower in the elderly, and in this patient population organic disorders must be excluded.

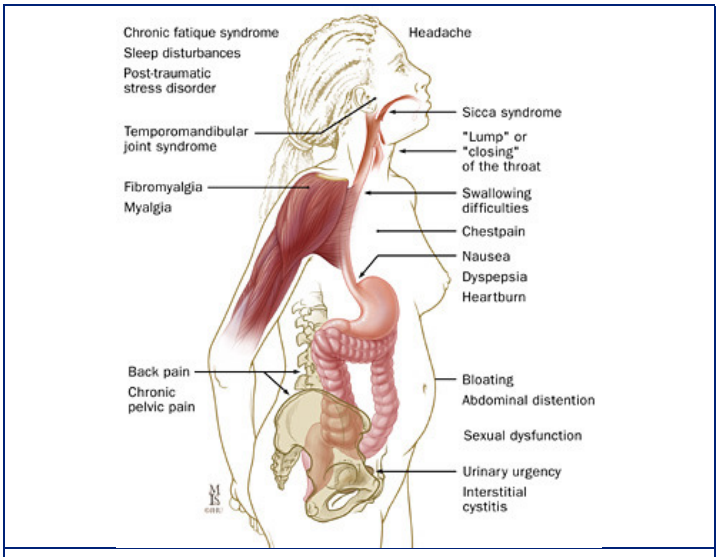

Figure 8. Symptoms and signs of Irritable Bowel Syndrome.

Symptoms unrelated to the intestine (extraintestinal symptoms) are common in patients with IBS. These may include headache, sleep disturbances, post-traumatic stress disorder, temporomandibular joint disorder, sicca syndrome, back/pelvic pain, myalgias, back pain, and chronic pelvic pain (Figure 8). Fibromyalgia and interstitial cystitis are also frequently encountered in patients with IBS. In fact, Fibromyalgia occurs in up to 33% of patients with IBS and almost half of patients with fibromyalgia also have IBS.

Irritable Bowel Syndrome (IBS): Anatomy

The lower gastrointestinal tract is divided into five parts: the cecum, the ascending colon, the transverse colon, the descending colon, and the rectum. The large intestine (colorectum) begins at the cecum, which is approximately 2–3 inches long and shaped like a pouch. Ileal contents empty into the cecum through the ileocecal valve. The appendix extends from the base of the cecum. The ascending colon rises from the cecum along the right posterior wall of the abdomen, under the ribs to the undersurface of the liver. At this point it turns toward the midline (hepatic flexure), becoming the transverse colon. The transverse portion crosses the abdominal cavity toward the spleen, then goes high up into the chest under the ribs, and turns downward at the splenic flexure. Continuing along the left side of the abdominal wall to the rim of the pelvis, the descending colon turns medially and inferiorly to form the S-shaped sigmoid (sigma-like) colon. The rectum extends from the sigmoid colon to the pelvic floor muscles, where it continues as the anal canal terminating at the anus (Figure 9). The anal canal is approximately 4 cm long.

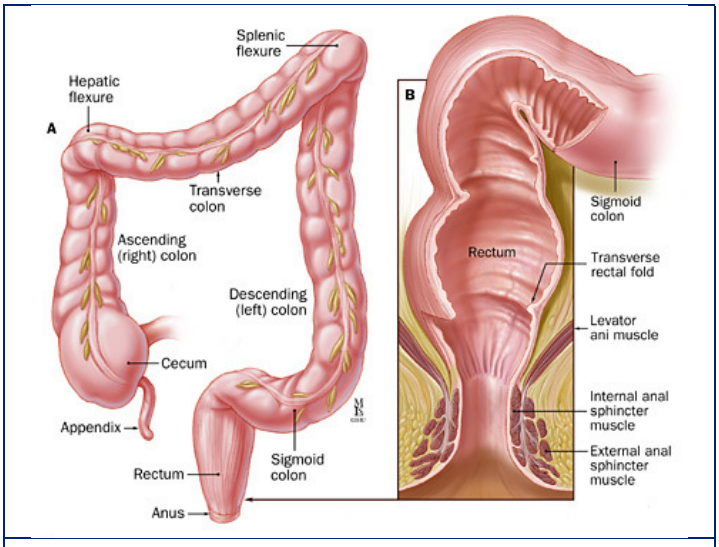

Figure 9. A, B: Normal anatomy of the colon and rectum

The large intestine, the site of salt and water absorption, is approximately 5–6 feet long and about 2½ inches in diameter. It is the site of salt and water absorption. Glands secrete large quantities of alkaline mucus into the large intestine, and the mucus lubricates intestinal contents and neutralizes acids formed by bacteria in the intestine. These bacteria aid in decomposition of undigested food residue, unabsorbed carbohydrates, amino acids, cell debris, and dead bacteria through the process of segmentation and putrefaction. Short-chain fatty acids, formed by bacteria from unabsorbed complex carbohydrates, provide an energy source for the cells of the left colon. Maintenance of potassium balance is also assigned to the colon, where the epithelium absorbs and secretes potassium and bicarbonate.

The sympathetic and parasympathetic nervous systems innervate the gastrointestinal tract (Figure 10). Both carry sensory stimuli, though it appears that spinal affrent nerves in the dorsal horn of the spinal cord process pain.

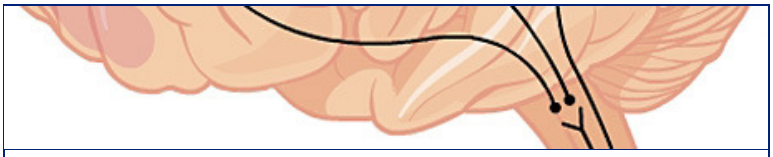

Figure 10. Sensory pathway in Irritable Bowel Syndrome, an animated sequence (To view, click on the image above).

Irritable Bowel Syndrome (IBS): Causes

Overview
Based on the writings of physicians and historians, functional disorders of the gastrointestinal tract have existed throughout history. Systematic investigation of these disorders, however, did not begin until the middle of the 20th century—and it is only within the last 20 years that physicians have developed a scientific understanding and concern for the treatment of patients with IBS. The most current research on the topic suggests a biopsychosocial model of the disorder, implicating physiological, emotional, behavioral and cognitive factors.

Psychosocial
Approximately 40–60% of patients with IBS who seek medical care also report psychiatric symptoms, such as depression, anxiety, or somatization. Interestingly, however, psychiatric symptoms in patients with IBS in the general population are not as prevalent. It is thought that these psychiatric disturbances influence coping skills and illness-associated behaviors. A history of abuse (physical, sexual, or emotional) has been correlated with symptom severity. More than half of patients who are seen by a physician for Irritable Bowel Disease report stressful life events coinciding with or preceding the onset of symptoms.

Stress is known to alter gastrointestinal function. Patients who suffer from IBS have amplified colonic motility responses when compared to normal volunteers (those who do not have any symptoms of IBS). Researchers believe the limbic system (an area of the brain where stress is perceived and experienced) is critically involved (Figure 11). Moderate stress in rats causes the release of corticotropin-releasing factor. Patients with IBS have an exaggerated colonic response to corticotropin-releasing factor and certain other drugs.

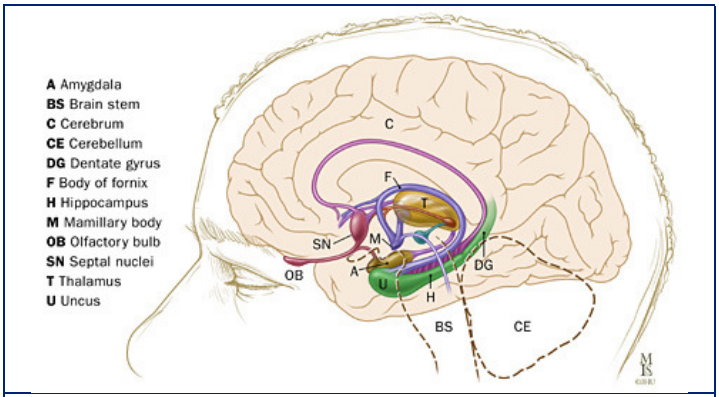

Figure 11. Anatomy of the limbic system.

Neurotransmitters
IBS patients demonstrate significant differences in pain perception, and a variety of perceptual abnormalities related to gastrointestinal stimuli may be more frequent in irritable bowel sufferers. This sensitivity develops as a result of visceral hyperalgesia. Studies evaluating somatic stimuli have demonstrated that the lower tolerance for pain in patients with IBS occurs primarily in the bowel.

Recent studies associate neurotransmitters with IBS. Serotonin is located in the central nervous system (5%) and the gastrointestinal tract (95%), and when it is released into the body it results in the stimulation of intestinal secretion and peristaltic reflex and in symptoms such as abdominal pain, bloating, nausea, and vomiting. These preliminary studies suggest increased serotonin levels in the plasma and in the rectosigmoid colon of patients with IBS.

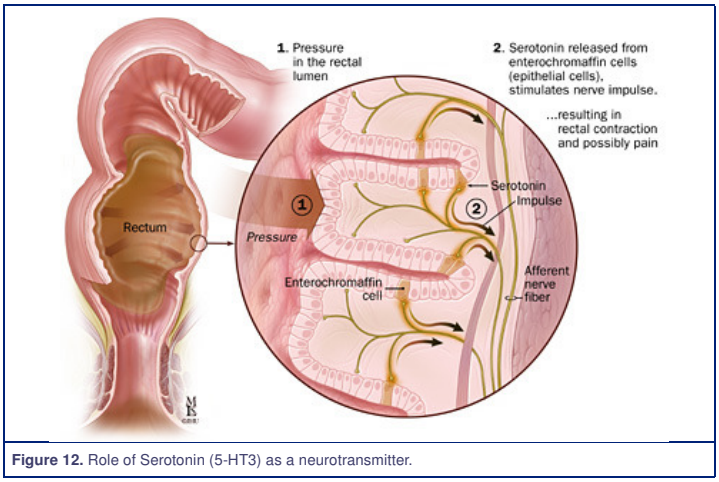

Figure 12. Role of Serotonin (5-HT3) as a neurotransmitter.

Infections
Other theories concerning IBS associate the inflammation of enteric mucosa or neural plexuses with symptoms. It is hypothesized that inflammatory cytokines may activate peripheral sensitization or hypermotility. One group of researchers was able to predict the development of IBS in patients with infectious enteritis in the presence of stressful life events and hypochondriasis. Researchers in Ontario recently demonstrated that post infection inflammation (Trichomonas spiralis) alters

visceral sensitivity. In this particular study, NIH Swiss mice were infected with T spiralis. Six days after infection the mice experienced jejunal enteritis, which returned to normal after 28 days. Using a latex balloon placed in the distal colon, investigators found hyperalgesic sensory response following distension that persisted despite the lack of acute inflammation.

Irritable Bowel Syndrome (IBS): Diagnosis

Clinical Criteria for Diagnosis
In the absence of definitive diagnostic physical findings or biological markers, the diagnosis of IBS rests on physician's recognition of classic clinical symptoms and the exclusion of other diseases. The presence of abdominal pain or discomfort is essential to the diagnosis of IBS.

To facilitate comparisons among different populations and assist in epidemiological studies of IBS, two sets of criteria for diagnosis have been developed—the Manning and Rome Criteria (Table 1).

A multinational working team subsequently developed the Rome Criteria. The original criteria, Rome 1, were recently revised and the new Rome 2 diagnostic criteria are included below. Recent research has demonstrated that Rome 1 and Rome 2 do not necessarily identify the same IBS patient. This has raised questions regarding the use of the criteria in clinical research and further study is needed.

Manning Criteria	
Includes six symptoms:	
Relief of abdominal pain with defecation	Bloating or abdominal distension
Looser stool with the onset of abdominal pain	Feeling of incomplete evacuation of stool
More frequent bowel movements with the onset of pain	Passage of mucus from the rectum
Rome II Criteria	
Twelve weeks or more, which need not be consecutive, in the preceding 12 months, of abdominal discomfort or pain that has two of the following three features:	
Relief with defecation	
Onset associated with a change in the frequency of stool	
Onset associated with a change in the form and appearance of stool	
The following symptoms are *not* essential for the diagnosis, but their presence increases the confidence in the diagnosis:	
Abnormal stool frequency (greater than 3 daily or less than 3 weekly)	
Abnormal stool form (loose/watery or lumpy/hard) in greater than 25% of defecations	
Abnormal stool passage (straining, urgency or feeling of incomplete evacuation) in greater than 25% of defecations	
Passage of mucus in greater than 25% of defecations	
Bloating or sensation of abdominal distension in greater than 25% of the days.	

Table 1. Criteria for the diagnosis of Irritable Bowel Syndrome

Diagnostic Approach
Effective diagnosis of IBS begins with a careful history and physical examination. The presence of "alarm symptoms" or "red flags" suggests more extensive evaluation for organic causes (Table 2).

ALARM SYMPTOMS	
Age greater than 50 years	Persistent or progressive pain
Unexplained weight loss	Family history of colon cancer
Anemia	Fasting, nocturnal or large volume (>300ml/day) diarrhea
Evidence of gastrointestinal bleeding	

Table 2.

The initial evaluation should also include: a complete blood count, chemistry panel, and erythrocyte sedimentation rate, and a stool test for fecal occult blood.

A colonoscopy should be performed in patients 50 years of age or older (a family history of colon cancer may warrant an earlier colonoscopy) and may detect organic disease in 1-2% of patients (Figure 12).

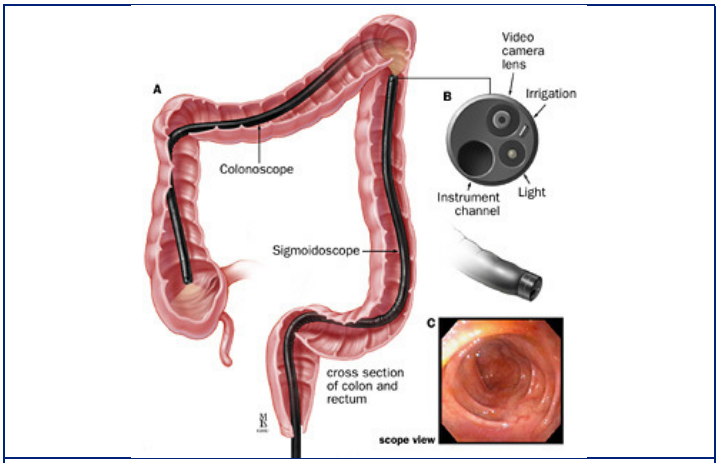

Figure 13. A, Colonoscope and sigmoidoscope examining the colon; B, Detail view of the scope tip; C, Scope image of the lumen of the colon

Measurement of thyroid-stimulating hormone is commonly performed and abnormalities have occasionally been found, but no studies have demonstrated improvement in IBS symptoms if these abnormal thyroid tests are treated.

Stool testing for Ova and Parasites are generally of low yield (0-2%) and the outcome of therapy on symptoms of IBS in patients with parasites is unknown.

The prevalence of lactose malabsorption in patients with IBS is about 25%, which is not significantly higher that the general population. It is unclear whether or not a lactose-free diet significantly improves the symptoms of IBS.

Further evaluation depends on the predominant clinical symptom—pain, constipation or diarrhea. Lactose (a sugar found in mammalian milk) malabsorption, celiac disease and other malabsorptive disorders should be considered in suspected patients (Table 3).

Suspected Disease	Diagnostic Test
Lactose Intolerance	"Milk Challenge", Hydrogen breath testing
Fructose Intolerance	Hydrogen beath testing
Celiac Disease	Antiendomysial antibody, small bowel biopsy
Crohn's Disease	Erythrocyte sedimentation rate, small bowel barium radiographs
Idiopathic Bile Salt Malabsorption	Trial of cholestyramine

Table 3. Malabsorption disorders and the corresponding diagnostic test(s).

Once a diagnosis of IBS has been made, attention should be shifted to treatment. Continued investigations due to persistent symptoms are not warranted and may ultimately undermine a patient's confidence in both the disorder diagnosis and the attending physician.

Irritable Bowel Syndrome (IBS): Therapy

Overview
Management of patients with Irritable Bowel Syndrome is based on a positive diagnosis of the syndrome, exclusion of organic disorders, and specific therapies. Treatment for IBS should address the three main pathophysiologically important factors—psychosocial disturbances, visceral hypersensitivity, and dysmotility. Treatment should be patient oriented and geared towards symptom –specific relief. The majority of conventional IBS treatments currently used is empiric and has not been formally reviewed and approved by the FDA. Therapies may include fiber consumption for constipation, anti-diarrheals, smooth muscle relaxants for pain, and psychotropic agents for pain, diarrhea and depression. Female patients with diarrhea predominant-IBS may benefit from alosetron, a new 5-HT3 agonist, while female patients with constipation predominant-IBS may benefit from Tegaserod Maleate, a partial 5HT4 agonist.

Patients with mild or infrequent symptoms may benefit from the establishment of a physician-patient relationship, patient education and reassurance, dietary modification, and simple measures such as fiber consumption. Patients with constipation-predominant IBS can generally be treated with osmotic mild laxatives such as Milk of Magnesia. Stronger laxatives should be reserved for patients who do not respond to fiber consumption and gentle osmotic laxatives.

Management Recommendations for Irritable Bowel Syndrome

Make a positive diagnosis based on symptoms and absence of alarm features (*see* Diagnostic Approach section, Table 2): many patients *do not need* colonic investigation.

Establish **effect of illness** and patient's **psychosocial resources** (e.g. family support).	**Avoid repeated tests** unless new development of structural disease is suspected–e.g. presentation with new alarm features.
Establish if there is a **comorbid psychiatric disease** or an **unresolved major loss or trauma.**	Center treatment on the principle of **patient-based responsibility of care**.
Provide **firm assurance**, emphasizing their symptoms are known to be real (not just "in their head") and that irritable bowel syndrome is a **recognized bowel disease**.	Set **realistic treatment goals**. Consider referral to a patients' **support group**.
Provide **education**, including an understandable explanation of **why symptoms might arise**, emphasizing that the patient is not alone in their suffering and the prognosis is **benign**.	Organize a **continuing care strategy** if symptoms have been chronic or disabling.
Assess the **patient's expectations and hidden fears**–e.g. find out why they have presented now, despite longstanding symptoms–and try to address all concerns.	Try **dietary modifications,** first-line–e.g. a low fiber diet for diarrhea and a cautious increase in fiber for those with constipation. Avoid obvious food precipitants.
Avoid giving mixed messages–e.g. by reassuring the patient, then ordering extensive tests without an adequate explanation.	**Prescribe drugs sparingly if possible**, targeting the symptoms of most concern to the patient and providing frequent drug holidays where feasible (with the exception of antidepressants).
With permission from: Tally NJ, Spiller R. Irritable bowel syndrome: a little understood organic bowel disease? *The Lancet* 2002; 360: 555-64.	**Consider psychological treatments** for those with moderate-to-severe symptoms.

Table 4. Management recommendations for Irritable Bowel Syndrome

Physician-Patient Relationship
Patients suffering from IBS often present for medical care only after frustrating self-diagnostic attempts to determine symptom causation and resolution. It is very important, therefore, that the responsible physician foster a positive relationship with the patient in order to aid in successful clinical management. A positive, confident diagnosis, accompanied by a clear explanation of possible mechanisms and an honest account of probable disease course, can be critical in achieving desired management goals. In order to facilitate a positive relationship, it is important that the physician practice the following principles:

- Reassure the patient that they are not unusual
- Identify why the patient is currently presenting
- Obtain a history of referral experiences
- Examine patient fears or agendas
- Ascertain patient expectations of physician
- Determine patient willingness to aid in treatment
- Uncover the symptom most impacting quality of life and the specific treatment designed to improve management of that symptom

In addition to addressing patient fears and concerns, physicians must evaluate whether or not the introduction of physician aids, such as dietitians, counselors, and support groups, may be of long-term assistance to the patient.

Patient Education
Patient education is essential to any successful management plan. In the case of IBS, this includes offering the patient a clear, easily comprehensible explanation of the pathophysiology of the disorder from which they are suffering, its causes and symptoms, as well as the role of psychosocial factors in its presentation. Patients presented with detailed discussions about their diagnosis and treatment options have reduced symptom intensity and fewer return visits. In order to best educate patients, physicians must speak to the following issues with the patient:

A. Incidence of IBS symptoms in the general population and its relevance to the patient
B. Gastrointestinal physiology including gastrocolonic response, production of gas, gut sensitivity to certain stimuli, and possible
C. The potential impact of stress in triggering or exacerbating symptoms, with reassurance that symptoms are not psychosomatic
D. Any anxieties, including concerns about underlying disease and major symptoms

E. The need for the patient to accept responsibility for condition management
F. The recognition that no panacea exits, but that therapies can greatly improve quality of life and significantly reduce symptom severity

Well informed patients are more apt to make choices and changes in lifestyle and diet that can reduce the severity and the frequency of their symptoms. It is recommended that physicians discuss new information during patient visits, and build on previous information by disseminating any new educational materials that may have become available since the patient's last visit.

Diet

Some symptoms of IBS are now understood to result from abnormal colonic fermentation subsequent to damaged gut flora by antibiotics or gastroenteritis. The excess production of hydrogen, along with a range of other compounds, is thought to impact colonic functioning. It has been demonstrated that patients with mild to moderate symptoms typically are most responsive to dietary modifications. In these patients diet and bulking agents may effectively manipulate colonic fermentation, resulting in successful IBS management.

Physicians should encourage patients with both constipation-predominant and diarrhea-predominant IBS symptoms to gradually incorporate fiber into their diets. Fiber gently stretches the bowel wall, decreasing tension. Fiber supplements such as bran, psyllium derivatives, or polycarbophil (20–30 grams/day) may aid in relief of constipation and may also improve symptoms of diarrhea. However, the efficacy of bulking agents has not yet been clearly established—despite the fact that they are widely prescribed.

Dietary modifications are the therapy of choice for patients with abdominal pain, diarrhea, flatulence and abdominal distension, with reported response rates of 50-70%. In these patients, certain foods can initiate or aggravate symptoms of IBS as evidenced by symptom occurrence after meals. Lactose (milk sugar), caffeine, fatty foods, gassy vegetables (i.e., broccoli or beans), foods containing sorbitol, wheat cereals, or alcohol may trigger symptoms. These foods should be avoided. To determine dietary triggers, patients should try an exclusion diet—restricting their diet to basic bland foods, gradually adding new foods and recording symptoms. Any food causing symptoms should be avoided. Elimination diets are intended for short-term use only as they are nutritionally deficient, and should be supervised by a dietitian or medical professional with experience in this field.

A daily food diary is another important tool in identifying trends in food or stress triggers. For each day of the week, patients should be encouraged to record the types of foods and beverages they have consumed, the number of bowel movements they have experienced, any pain they have experienced (on a scale form 1-10), their mood while eating, the time of day for each variable and any other relevant symptoms (Figure 14). Food diaries should be as specific as possible (i.e. noting food preparation and condiments), honest in reporting every food and beverage consumed, and updated throughout the day. The diary should be brought to physician visits for review in order to provide valuable information about potential relationships between dietary triggers and symptoms.

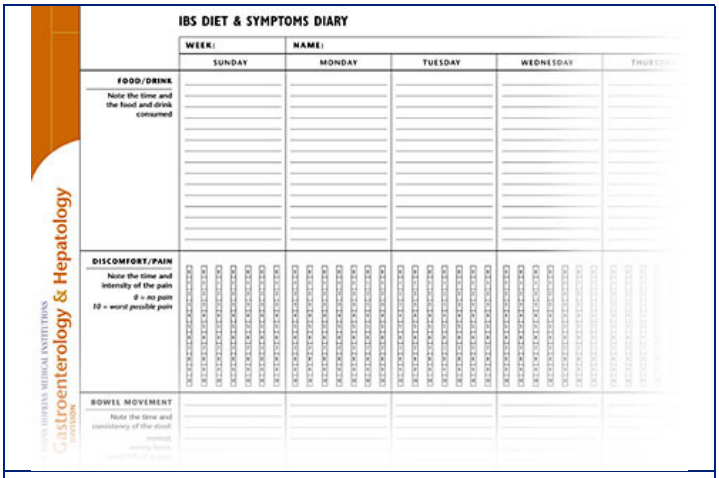

Figure 14. Daily food diary (To view the complete printable PDF version, click on the image above).

Dairy products are the most common dietary triggers of gas, bloating, and occasional abdominal pain. A lactose breath hydrogen test, measuring the spike of breath hydrogen when malabsorbed lactose enters the colon, is the definitive test for lactose intolerance. While lactose intolerant patients should avoid consumption of milk and milk products (cheese, ice cream, and butter), it remains unclear whether or not a lactose-free diet demonstrates symptom resolution. One explanation for this may be that subjective lactose intolerance is increased in patients with IBS even though there is no increase in the prevalence of lactose maldigestion. Other research speculates that patients who are lactose intolerant may experience improvement not solely by abstaining from dairy, but by adhering to a fully exclusionary diet. Therefore, there appears to be little benefit in separating lactose malabsorbers from others with IBS. Instead, physicians should encourage all patients with IBS to try an exclusion diet. In cases where milk products are reduced, care must be taken that enough calcium is added to the diet through either foods high in calcium, or a calcium supplement.

The sweeteners, fructose and sorbitol may produce symptoms similar to those of lactose intolerance. The sugar sorbitol is only passively absorbed in the small intestine, and in clinical studies 10 g doses produced symptoms identical to lactose malabsorption in about half the patients tested. Fructose alone, or in combination with sorbitol, may produce significant symptoms in IBS patients. One study found that fructose-sorbitol malabsorption is frequently seen in IBS patients, but this result did not differ from the observation of fructose-sorbitol malabsorption in healthy volunteers. The authors concluded that this type of malabsorption does not seem to play an important role in the etiology of IBS. However, several other researchers argued this conclusion by suggesting that some patients do react adversely to sorbitol-fructose intake (especially those with diarrhea). Generation of symptoms could therefore be related to both the nature of colonic fermentation and individual sensitivity. High levels of sorbitol are found in apples, pears, cherries, plums, prunes, peaches and their juices. Dietetic foods and pharmaceuticals may also contain added sorbitol. Honey, all fruits and many processed foods contain high levels of fructose. Reducing or eliminating foods containing these products may be considered as part of an elimination diet.

Some patients with IBS may experience an aggravation of symptoms with the consumption of wheat and gluten-related products. Many patients with diarrhea-predominant IBS respond well to a short-term gluten- or wheat-free diet. This means eliminating all products that might contain wheat and wheat flour, as well as other offending grains such as rye, oats and barley. Elimination of these products need not be lifelong, but adjusted according to symptom occurrence.

Probiotics (e.g. yogurts, acidophilus supplements) have been found to be helpful to some patients. A lactobacillus supplement may help return the balance of microflora in the bowel to normal, thereby significantly reducing IBS symptoms. Researchers suggest that lactobacillus supplement works by preventing disease-causing bacteria from attaching to the bowel wall.

In general, patients should be encouraged to adhere to a healthy, well-balanced diet avoiding foods that aggravate symptoms. IBS patients should also be encouraged to eat slowly, avoid gum and artificial sweeteners, as well as caffeinated and carbonated beverages. Patients should be referred to a dietitian for additional assistance in menu planning if necessary.

Psychotherapy

A history of stressful life events or a current distress often precedes development of IBS. In several clinical studies it has been demonstrated that the onset of psychiatric disorders occurs prior to, or concurrent with, IBS symptom onset. When determining treatment for a patient with IBS, physicians should inventory: psychological distress, including the existence of anxiety or depressive disorder; personality characteristics, including a strong propensity to worry, possibly regarding health concerns; current social stresses and inadequate coping mechanisms; and abnormal illness behavior.

Of all psychiatric symptomology, IBS patients most frequently present with depression and anxiety. While these disorders typically respond well to treatment, left unchecked they can compromise clinical IBS management as well as exacerbate bowel symptoms. Psychiatric referral is recommended whenever the physician believes further assessment is in the patient's best interest, for example when the patient is depressed and expresses suicidal ideation or when the patient has questions regarding psychotropics. Additionally, psychiatric referral is warranted when there is serious social impairment not related to IBS, when there is repeated somatization with referral to various departments, or if a history of abuse or any major trauma is uncovered.

Several psychological interventions have been suggested for the treatment of IBS, including psychotherapy. Cognitive Behavioral Therapy (CBT) has shown promise for patients with moderate to severe IBS and those with IBS and concomitant anxiety or mood disorders. CBT can help patients learn coping strategies to control the symptoms brought on by anxiety or preoccupation. In Cognitive Behavioral Therapy, IBS patients work with a therapist to address specific concerns and perceptions about their functional gastrointestinal symptoms. These perceptions are modified in ways that lead to changes in cognitive appraisal of stress, which in turn impacts the patient's bowel symptoms. Additionally, CBT teaches patients how to recognize situations that may trigger their IBS symptoms. As a result, patients can learn how to find healthier ways of responding to those situations, thereby reducing stress. Combination therapy—medical management plus psychotherapy—has, in recent research, demonstrated great success, and may represent the future of IBS treatment.

Stress Management

Given the connection between the nervous system and colonic function, it is clear that stress plays a role in the frequency and severity of symptoms in patients with IBS. Patients should be encouraged to recognize and accept stressors in their lives. Breathing techniques and physical activity have proven useful in alleviating or helping patients deal with stress in their lives. Biofeedback and relaxation techniques, such as imagery or self-hypnosis, encourage control of physical and emotional responses—especially when coping with stress.

A diary may help patients recognize stressors that activate symptoms. The diary should include the date and time, the symptom experienced and its severity (for example, pain or diarrhea on a scale of 1-10), associated factors (such as diet, activity or stress), emotional response (angry, sad, anxious), and thoughts associated with the incident (out of control, hopeless). A written record of stressors and associated responses may help patients more easily identify triggers and more rapidly implement appropriate stress management techniques.

Drug Therapy

Smooth muscle relaxants

Recent clinical trials of anticholinergic and antispasmodic agents have shown these drugs to be significantly more efficacious than placebo in relieving IBS symptoms. However, it should be noted that these trials have been criticized for methodological failings, and the efficacy of anticholinergics and antispasmodics has not yet been proven definitively. As a result, these drugs are only recommended on an "as needed" basis, with dosing up to twice a day for bloating, distention and acute attacks of pain. Mebeverine and Dicyclomine appear to lose their effectiveness with chronic use. Currently available antispasmodics are separated into the general therapeutic classifications of anticholinergics, calcium-channel blockers, and opiod receptor modulators.

The most commonly prescribed anticholinergics in the U.S. are dicyclomine, hyoscyamine, and clidinium (in combination with chlordiazepoxide hydrochloride (Librium) = Librax). Gut-selective calcium-channel blockers, used to regulate movement of calcium ions into smooth muscle cells and neurons, have been developed to treat IBS and to avoid the undesired cardiovascular and systemic effects of traditional calcium-channel blockers. Peppermint oil, a carminative long utilized to treat IBS pain, has seen inconsistent outcomes. Opiates such as trimebutine have often been used not only as antidiarrheals but also as antispasmodics. Newer classes of antispasmodics (neurokinin [NK]2 receptor antagonist and ß3-adrenoceptor agonists) are in phase II clinical trials.

Antidiarrheal agents

Antidiarrheal agents are used to treat diarrhea adjunctly with rehydration therapy to correct fluid and electrolyte depletion. In patients with diarrhea as the predominant symptom, small bowel and proximal colonic transit times are accelerated. Loperamide (2–4 mg up to 4 times/day) decreases transit time, enhances bile acid absorption, increases anal sphincter tone, and reduces abdominal pain. This synthetic opioid is also effective in reducing postprandial urgency and improving control at times of anticipated stress. Loperamide is preferable to other narcotics for treating irritable bowel patients with diarrhea and/or incontinence. Cholestyramine may also be useful as a second or third line treatment for bile acid malabsorption.

Psychotropic agents

In the subset of patients with pain and diarrhea as the predominant symptoms of IBS, tricyclic agents have been found to be particularly beneficial (Table 5). This therapy is typically recommended in patients with severe symptoms, or symptoms resistant to first-line approaches, due to side effects. Lower dosages are used compared with dosages used for the treatment of depression

Tricyclic agents function as analgesics by modulating pain via their anticholinergic properties. It is hypothesized that tricyclic antidepressants directly influence brain-gut axis abnormalities inherent to the function process. Initially, a low dose is administered, and subsequently the dose is titrated to control pain. In addition, low doses have been found to slow orocecal transit, potentially replacing antidiarrheals in diarrhea-predominant patients. Because of the delayed onset of action, 3 to 4 weeks of therapy should be attempted before considering a dose insufficient. Amitriptyline, at a starting dose of 10 to 25 mg daily, or imipramine, at 25 to 50 mg daily, is useful for this purpose. Certain tricyclic agents, such as amitriptyline, may be particularly helpful for patients who complain of insomnia or who have well-defined depression or panic attacks.

Tricyclic antidepressants can cause or aggravate constipation, and should thus be avoided in patients with constipation-predominant IBS. These agents are also unsafe to use in patients who are pregnant. As in the case of any drug therapy, patients should be warned about anticholinergic side effects (see chart below).

Selective Serotonin Reuptake Inhibitors

While there have been few randomized trials conducted to gauge the effectiveness of serotonin reuptake inhibitors (SSRIs: paroxetine, fluoxetine and sertraline), these drugs do appear to be beneficial at typical psychiatric dosages (Table 5). The newer SSRIs, in particular Zoloft and Effexor, may be preferable in older patients or in those with constipation, because they are associated with fewer anticholinergic side effects. Citalopram was given to patients in a well-conducted small study in Belgium. The results of this study demonstrated that the drug induced a small degree of colonic relaxation, increased colonic tone and reduced the degree of discomfort associated with colonic distention.

It is believed that SSRIs impact IBS symptoms through a different mechanism than tricyclic antidepressants. In a small, retrospective review of patients receiving SSRIs for psychiatric treatment, the addition of tricyclic antidepressants improved gastrointestinal functioning. As a result, it is thought that SSRIs may impact IBS by modifying the cognitive environment and the patient's sense of well-being. Early results from a recent study report that paroxetine also improved global measures in patients with severe IBS. In this study, in contrast to research using low-dose tricyclic antidepressants, a correlation was found between paroxetine use and reduction of psychological ratings. It has been suggested, therefore, that reduced anxiety and depression may result in positive outcomes in global well-being, which may generalize to secondary positive effects on IBS.

There is growing interest in this class of drugs and their potential in the treatment of IBS. Due to the lack of large trials using these agents, however, additional research is needed to determine their effectiveness in the treatment of IBS.

Drug summary table

Generic Name	Dosage	Common Side Effects
Tricyclic Antidepressants (Class)		
Amitriptyline	25 mg 2-4 times daily to start, not to exceed 150 mg q.d.	Dizziness, drowsiness, dry mouth, headache, increased appetite, tiredness, nausea, unpleasant taste, weight gain, diarrhea, heartburn, sweating, trouble sleeping, vomiting
Doxepin	25 mg t.i.d. to start, not to exceed 150 mg q.d.	Same as above
Clomipramine	25 mg q.d.to start, not to exceed 250 mg q.d.	Same as above
Nortriptyline	25 mg 3-4 times daily to start, not to exceed 150 mg q.d.	Same as above
Trimipramine	75 mg q.d. to start, not to exceed 200 mg q.d.	Same as above
Desipramine	100-200 mg q.d. not to exceed 300 mg q.d.	Upset stomach, drowsiness, weakness or tiredness, anxiety, insomnia, nightmares, dry mouth, sunlight sensitivity, changes in appetite or weight
Imipramine	25-50 mg 3-4 times daily, not to exceed 200 mg q.d.	Same as above
5 HT3 Agonists		
Ondansetron	8 mg q 12 h	Constipation, diarrhea, fever, headache, abdominal pain or cramps, burning or tingling sensation, dizziness, drowsiness, dry mouth, itching, weakness or tiredness
Granisetron	1-2 mg q.d.	Abdominal pain, constipation, diarrhea, headache, tiredness or weakness, agitation, dizziness, drowsiness, heartburn, indigestion, trouble sleeping, unpleasant taste
Alosetron	1 mg b.i.d.	Constipation, abdominal pain or cramps, fever, rectal bleeding, watery or bloody diarrhea
5HT4 Agonists		
Tegaserod	6 mg b.i.d.	Diarrhea, flatulence, nausea, headache
Prucalopride	--	--
Antiserotonin Agents		
Mianserin	--	Hypersensitivity reaction, nausea, drowsiness, jaundice, may precipitate seizures, blood dyscrasias, lethargy, tremors
Opiod Agonists		
Fedotozine	40 mg q.d.	--

Table 5. Drugs used for the treatment of Irritable Bowel Syndrome

Alternative Therapy

Alternative therapies have been found to be useful for some patients. Herbs, including chamomile, ginger and mint have been found to be helpful in alleviating gastrointestinal pain in a subgroup of patients. One particular Chinese herb, which is made up of 20 herbs, has demonstrated efficacy in a formal clinical trial. Patients should understand that some herbs can interact negatively with prescribed or over-the counter medications and information about the use of any complimentary medicine should be shared with the responsible physician.

Some patients report symptom improvement from meditation and biofeedback therapies. Still others have achieved a degree of success and relief from symptoms with relaxation therapy. Several small studies suggest acupuncture provides significant relief from chronic pain. In IBS patients, there are reports that acupuncture can relax muscle spasms and improve bowel function.

Hypnotism is another alternative therapy gaining attention for the treatment of IBS. Hypnotism may help IBS patients manage stress and anxiety and enhance coping skills. By focusing the patient on the physiology of the gut through visualization techniques, colonic motility and visceral sensitivity may be modified. Several randomized controlled trials have demonstrated improvement in bowel function, pain, abdominal distention and global well-being associated with hypnosis. While this type of therapy is more expensive than traditional medications, symptom cessation may be longer-lasting than with other agents.

Other alternative therapies used to treat IBS include pro-flora supplements such as acidophilus and lactobacillus species, taken two to three times per day, to rebalance normal bowel bacteria and reduce gas and bloating. Regular exercise, such as walking, can reduce stress and encourage bowel movements. Therapeutic massage may help in reducing the effects of stress. No well-designed studies have evaluated the effect of chiropractic treatments on individuals with IBS, but it has been reported that spinal manipulation may improve symptoms of the condition in some individuals. It is hypothesized that in these cases, spinal manipulation may have a balancing effect on the nerves that supply impulses to the intestinal tract.

The current integrated understanding of IBS as a biopsychosocial entity has led to the use of psychological treatments, which have shown benefits in several

well-designed studies. Cognitive Behavioral Therapy, dynamic/interpersonal psychotherapy, hypnotherapy and stress management training (relaxation and biofeedback) have all been studied. These strategies should be offered to patients with disabling symptoms, associated psychiatric disorders, and abuse history, although patients with less severe symptoms may also benefit.

An integrated approach that views IBS as a biopsychosocial illness is effective in most patients. The biopsychosocial model offers a framework that helps both the physician and the patient understand the interaction of physical and psychosocial factors and their contribution to illness. This model serves as a basis for the current state-of-the-art approach to the diagnosis and management of IBS and also provides a rationale for the development of future treatment modalities.

Newer Therapy Options

Overview

Several novel treatment approaches are currently being studied. 5HT3 antagonists (such as alosetron) have been found to diminish visceral sensitivity and slow colonic transit. Alosetron has been shown to improve pain and bowel habits in women with diarrhea-predominant IBS. 5HT4 agonists (tegaserod and prucalopride), M3 muscarinic receptor antagonists (zamifenacin and darifenacin), and cholecystokinin (CCK) receptor antagonists (loxiglumide) appear promising for relief of constipation-predominant IBS and are currently in clinical trials. Tegaserod has been shown to improve pain and bowel habits in women with constipation-predominant IBS. New therapeutic approaches also target abnormal visceral sensitivity. These agents include 5HT3 antagonists, 5HT1 agonists (Buspirone), kappa-opioid agonists (fedotozine) and alpha-2 adrenergic agonists (Clonidine). These agents seem to reduce gut sensation in addition to altering motility (Figure 15).

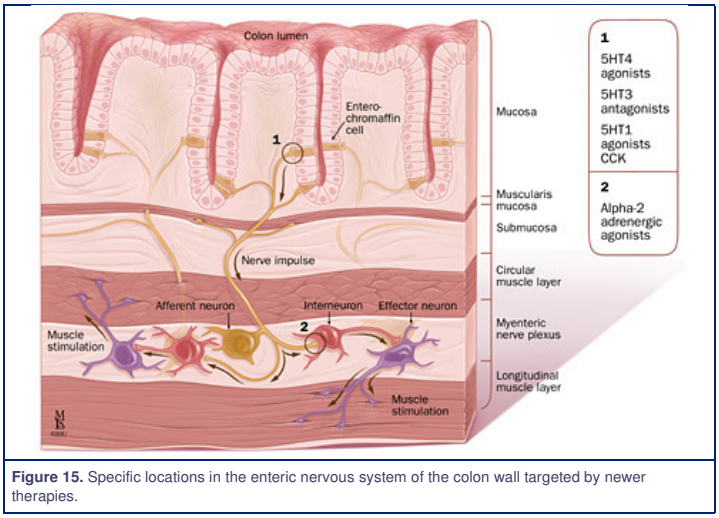

Figure 15. Specific locations in the enteric nervous system of the colon wall targeted by newer therapies.

Lotronex™ (Alosetron Hydrochloride) tablets
Pregnancy Category: B

WARNING: Serious bowel side effects, including some deaths, have been reported with the use of Lotronex™. These events include ischemia, colitis, and serious complications of constipation, which may lead to hospitalization. Only physicians who have been qualified by GlaxoSmithKline's Prescribing Program are permitted to treat patients with Lotronex™, and patients must sign a Patient-Physician Agreement with their doctor.

Actions/Kinetics: Lotronex™ is a potent and selective 5HT 3 receptor antagonist, which inhibits activation of enteric neurons in the human gastrointestinal tract that cause pain and constipation in IBS. The 5HT3 antagonists diminish visceral sensitivity and slow colonic transit. Taken orally, Lotronex™ is quickly absorbed with a mean bioavailability of approximately 50% to 60%. Following oral administration of a 1.0 mg Lotronex™ dose to young women, the mean peak plasma concentration is approximately 9ng/mL after 1 hour. Renal elimination of unchanged Lotronex™ accounts for only 6% of the dose. Renal clearance is approximately 9ng/mL/min. Alosetron is extensively metabolized in humans, with only 7% of a radiolabeled dose recovered as unchanged drug.

Uses: Lotronex™ is indicated only for women with severe diarrhea-predominant IBS of at least 6 months duration, who have not responded to conventional therapy and have symptoms that include frequent and severe abdominal pain and frequent bowel urgency/incontinence that causes disruption of daily activities.

Contraindications: Lotronex™ is contraindicated in patients with:

- Crohn's disease, ulcerative colitis, or diverticulitis
- A history of ischemic colitis, compromised intestinal circulation, thrombophlebitis and other clotting disorders
- A histtory of severe or chronic constipation with subsequent problems/complications
- A history of intestinal obstruction, toxic megacolon, stricture, and gastrointestinal adhesions or perforation.

Side Effects: GI: Acute ischemic colitis, constipation, nausea, GI discomfort and pain, abdominal discomfort and pain, GI gaseous symptoms, viral gastrointestinal infections, dyspeptic symptoms, abdominal distension, hemorrhoids. Otolaryngology: Throat and tonsil discomfort and pain, allergic rhinitis, bacterial ear, nose, and throat infections. Cardiovascular: Hypertension. CNS: Sleep disorders. Psychiatry: Depressive disorders.

Risk of Side Effects

Ischemic colitis has been reported in patients receiving Lotronex™ in clinical trials as well as during marketed use of the drug. In IBS clinical trials, the cumulative incidence of ischemic colitis in women receiving Lotronex™ was 2 per 1,000 patients (95% confidence interval 1 to 3) over 3 months and was 3 per 1,000 patients (95% confidence interval 1 to 4) over 6 months. Patient experience in controlled clinical trials is insufficient to estimate the incidence of ischemic colitis in patients taking Lotronex™ for longer than 6 months.

Infrequent adverse events, those occurring on one or more occasion in 1/100 to 1/1000 patients include; rare adverse events are those occurring on one or more occasion in fewer than 1/1000 patients. These events include:

Blood and Lymphatic: Rare: Quantitative red cell or hemoglobin defects, hemorrhage, and lymphatic signs and symptoms.

Cardiovascular: Infrequent: Tachyarrhythmias. *Rare:* Arrhythmias, increased blood pressure, and extrasystoles.

Drug Interaction, Overdose, and Trauma: Rare: Contusions and hematomas.

Ear, Nose, and Throat: Rare: Ear, nose, and throat infections; viral ear, nose, and throat infections; and laryngitis.

Endocrine and Metabolic: Rare: Disorders of calcium and phosphate metabolism, hyperglycemia, hypothalamus/pituitary hypofunction, hypoglycemia, and fluid disturbances.

Eye: Rare: Light sensitivity of eyes.

Gastrointestinal: Infrequent: Hyposalivation, dyspeptic symptoms, gastrointestinal spasms, ischemic colitis and gastrointestinal lesions. *Rare:* Abnormal tenderness, colitis, gastrointestinal signs and symptoms, proctitis, diverticulitis, positive fecal occult blood, hyperacidity, decreased gastrointestinal motility and ileus, gastrointestinal obstructions, oral symptoms, gastrointestinal intussusception, gastritis, gastroduodenitis, gastroenteritis, and ulcerative colitis.

Hepatobiliary Tract and Pancreas: Rare: Abnormal bilirubin levels and cholecystitis.

Lower Respiratory: Infrequent: Breathing disorders. *Rare:* Viral respiratory infections.

Musculoskeletal: Rare: Muscle pain; muscle stiffness, tightness and rigidity; and bone and skeletal pain.

Neurological: Infrequent: Hypnagogic effects. Rare: Memory effects, tremors, dreams, cognitive function disorders, disturbances of sense of taste, disorders of equilibrium, confusion, sedation, and hypoesthesia.

Non-site Specific: Infrequent: Malaise and fatigue, cramps, pain, temperature regulation disturbances. *Rare:* General signs and symptoms, non-specific conditions, burning sensations, hot and cold sensations, cold sensations, and fungal infections.

Psychiatry: Infrequent: Anxiety. *Rare:* Depressive moods.

Reproduction: Rare: Sexual function disorders, female reproductive tract bleeding and hemorrhage, reproductive infections, and fungal reproductive infections.

Skin: Infrequent: Sweating and urticaria. *Rare:* Hair loss and alopecia; acne and folliculitis; disorders of sweat and sebum; allergic skin reaction; eczema; skin infections; dermatitis and dermatosis; and nail disorders.

Urology: Infrequent:
Urinary frequency. *Rare:* Bladder inflammation; polyuria and diuresis; and urinary tract hemorrhage.

Postmarketing Experience: The following events have been identified during use of Lotronex™ in clinical practice. Because they were reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been chosen for inclusion due to a combination of their seriousness, frequency of reporting, or potential causal connection to Lotronex™.

Gastrointestinal: Constipation, ileus, impaction, obstruction, perforation, ulceration, ischemic colitis, small bowel mesenteric ischemia

Neurological: Headache.

Skin: Rash.

DRUG ABUSE AND DEPENDENCE: Lotronex™ has no known potential for abuse or dependence.

Special Concerns:
Hepatic Insufficiency: Lotronex™ is metabolized primarily in the liver; therefore increased exposure to Lotronex™ and its metabolites is likely to occur in patients with hepatic insufficiency.

Geriatric Use: Elderly patients may be at greater risk for complications of constipation.

Drug Interactions: Based on data from in vitro and in vivo studies, it is unlikely that alosetron will inhibit the hepatic metabolic clearance of drugs metabolized by the major CYP enzyme 3A4, as well as the CYP enzymes2D6, 2C9, 2C19, 2E1, or 1A2.

Overdose Management: There is no specific antidote for overdose of Lotronex™. However, individual oral doses of 16 mg have been administered in clinical studies without significant adverse events (usual dose is 2mg).

Dosage and Administration: In order to prescribe Lotronex™, physicians must be enrolled in the GlaxoSmithKline Prescribing Program. Lotronex™ should be started at a dosage of 1 mg orally once a day for 4 weeks. If it is well tolerated but does not adequately control IBS symptoms, then the dosage may be increased to 1 mg twice a day. Lotronex™ should be discontinued if IBS symptoms are not adequately controlled after 4 weeks of therapy of 1 mg twice daily. Lotronex™ should be discontinued in patients who develop constipation or symptoms of ischemic colitis.

Prescribing Program for Lotronex™
Physicians must enroll in the Prescribing Program for Lotronex™, which is a component of the Risk Management Program. Physicians must complete a revised indication that reflects the intent to reserve Lotronex™ for patients in whom the medical benefits outweigh the risks, namely, women with severe diarrhea-predominant IBS. These changes are reflective of the serious gastrointestinal adverse events, some fatal, that have been reported with its use. Only physicians enrolled in the GlaxoSmithKline Prescribing Program may prescribe Lotronex™. For more information visit: http://www.fda.gov/cder/drug/infopage/lotronex/lotronex.htm, the Lotronex Web Site or call 1-888-825-5249.

Once a physician is enrolled in the Prescribing Program by confirming qualifications, acknowledging described responsibilities, and submitting the Physician Attestation Form, they will receive a prescribing kit from GlaxoSmithKline. When a potential patient is identified using the Package Insert criteria, the physician will counsel them on the use of Lotronex™, review the Medication Guide, and provide the patient with a copy of the guide. At this point, both the physician and patient sign the Agreement Form and provide the patient with a copy of the form. The original Agreement Form is placed in the patient's medical record. A Prescribing Program sticker is then affixed to the prescription and the patient is encouraged to enroll in the Lotronex™ Follow-up Survey.

In order for the patient to fill the prescription and any refills, the Prescribing Program Sticker must be on the prescription. No telephone, fax or computer-generated prescriptions for Lotronex™ will be filled. If no sticker is present, the patient will be referred back to the physician. Once the prescription is filled, the patient will be given a Retail Pack containing the Medication guide, Package Insert, Medicine, and the Follow-up Survey. At this time, the pharmacist will once again encourage the patient to enroll in the follow-up survey.

Zelnorm™ (Tegaserod Maleate)
Tegaserod is a partial 5HT4 agonist, one of a class of new drugs with promise in treating IBS. Patients marked by chronic constipation may experience relief with the drug's pro-motile properties and modulating effect on visceral sensitivity. Tegaserod has been approved by the FDA for the short-term treatment of women who have IBS, with constipation as their main symptom.

Clinical Results: Three multicenter, double blind, placebo-controlled studies evaluated Tegaserod in 2,470 women with IBS symptoms, namely abdominal pain, bloating and constipation. Two studies were fixed dose studies and the third was a dose-titration study. In all three studies, Tegaserod was administered for 12 weeks and efficacy was evaluated based on patients' ratings of their relief of symptoms and the intensity of symptoms. Tegaserod-treated patients reported greater relief from symptoms and a greater increase in number of stools than placebo-treated patients, with the largest difference during the first four weeks.

Pregnancy Category: B

Actions/Kinetics: Tegaserod is a partial agonist that binds with high affinity at human 5-HT4 receptors, and has no appreciable affinity for 5-HT3 or dopamine receptors. There is moderate affinity for 5-HT1 receptors. By acting as an agonist at neuronal 5-HT4 receptors, the release of further neurotransmitters such as calcitonin gene-related peptide from sensory neurons is triggered. The activation of 5-HT4 receptors in the gastrointestinal tract stimulates peristaltic reflex and intestinal secretion, as well as inhibiting visceral sensitivity. Fasting oral bioavailability is approximately 10% and administration with food reduces bioavailability by

>40%. Peak plasma concentration is obtained in 1 hour. The medication is 98% protein bound and highly lipophilic, with extensive tissue distribution. Tegaserod is metabolized via GI hydrolysis and hepatic glucuronidation. With no active metabolites, it has a half-life of 11 hours.

Uses: Tegaserod has been approved by the FDA for the short-term treatment of women who have IBS with constipation as their main symptom.

Insufficient data exists to support Tegaserod use in other populations, including men with IBS. Efficacy has not been studied beyond 12 weeks.

Dose: 6 mg PO BID before meals for 4-6 weeks. If a positive response is achieved, an additional 4-6 weeks can be considered.

Monitoring: Relief of constipation should be demonstrated, with diarrhea the most common side effect. During episodes of diarrhea lasting >2 days, periodically monitor electrolyte levels (sodium, potassium, chloride, bicarbonate).

Contraindications: Tegaserod is contraindicated in patients hypersensitive to the drug and in those with a history of bowel obstruction, gallbladder disease, and severe renal impairment, moderate to severe hepatic impairment, abdominal adhesion, and suspected sphincter of Oddi dysfunction. Caution should be exercised in patients with diarrhea and in pregnant and breast-feeding patients.

Interactions: None reported.

Special Concerns: Diarrhea may occur; do not give to patients with diarrhea; discontinue if new or sudden worsening of abdominal pain or diarrhea occurs

Side Effects: Adverse events associated with the use of Tegaserod may include (but are not limited to) the following:
CNS: Headache, dizziness, migraine.
GI: Abdominal pain, nausea, diarrhea, flatulence.
Musculoskeletal: Back pain, arthropathy, and accidental injury.
Other: Leg pain.

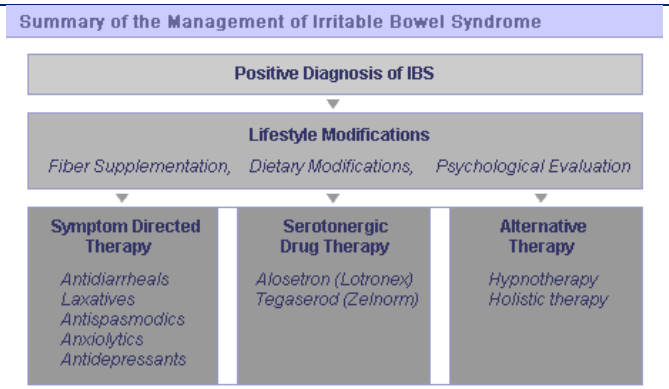

Table 6. Treatment Algorithm