Turmoil Within: Perspectives on Irritable Bowel Syndrome

by John H. Dirckx, M.D.

The past two centuries have witnessed the steady evolution of Western medicine from a welter of confusion, ignorance, superstition, and hit-or-miss empiricism into a scientific discipline based on objective data, rigorous logic, diagnostic precision, and evidence-based therapy. During that period many diseases have come to be clearly delineated, their causes exactly traced, diagnostic and treatment guidelines established, and preventive strategies worked out.

Yet a stubborn residue of enigmatic conditions, many of them hovering on the borderline between purely organic and psychosomatic disorders, remains to mock all efforts at scientific analysis and management. Irritable bowel syndrome (IBS) is one such, a disease with an ambiguous clinical picture, entirely lacking in pathognomonic symptoms or signs, organic lesions, laboratory markers, or fully satisfactory treatments.

For many decades the medical profession has struggled to pin down this ill-defined clinical entity, to find a unitary cause, to establish valid diagnostic criteria, and to develop safe and consistently effective therapies. Although the difficulty of defining the condition lies at the very heart of its elusiveness, most authorities would agree that it is a symptom complex characterized by

- chronic or recurrent abdominal pain,
- bloating (distention of the bowel with gas), and
- disturbance of bowel function,
- in the absence of any demonstrable organic lesion.

This is not an arcane disorder of purely academic interest. Irritable bowel syndrome of varying severity affects 15-20% of adolescents and adults in this country and accounts for 3 million physician visits a year: 10% of all visits to primary care physicians and 25-50% of all visits (including self-referrals) to gastroenterologists. IBS is easily the most frequent diagnosis made by gastroenterologists. Yet it is estimated that as many as 70% of persons who meet diagnostic criteria for the disorder never seek treatment for it.

The annual cost of IBS to American society, including direct medical charges and losses due to absenteeism from work and other forms of nonproductiveness, has been placed at $20-30 billion. The out-of-pocket medical expenses of IBS patients average about 50% more than those of persons without IBS, and the diagnosis is associated with about a 35% reduction in productivity on the job.

For most patients, IBS is a chronic, indeed lifelong condition. Symptoms may persist indefinitely, but typically they occur in episodes lasting days or weeks and separated by intervals of remission lasting days, weeks, months, or years. The pattern of symptoms can vary considerably from person to person, but each patient's pattern tends to remain stable throughout life.

The chief complications of IBS are chronic emotional distress (anxiety and depression), impaired quality of life, and unnecessary abdominal surgery (especially cholecystectomy and hysterectomy) prompted by misdiagnosis.

Pain, variably described as bloating or cramping, is usually felt in the lower abdomen or periumbilical area. It may be moderately severe but is seldom excruciating.

Disturbances of bowel function are an essential part of the syndrome. Some patients suffer chiefly from constipation (IBS-C), some chiefly from diarrhea (IBS-D), and some have both symptoms alternately (IBS-A). About one third of IBS patients fall into each of these categories. Patients often find that abdominal pain is relieved temporarily by a bowel movement, but many complain of the sensation that defecation doesn't effectively empty the lower bowel. Stools are often accompanied by an excessive secretion of mucus, hence the old-fashioned misnomer *mucous colitis*.

IBS does not impair the digestion or absorption of nutrients. It is not associated with increased mortality and it does not herald the onset of inflammatory bowel disease or gastrointestinal (GI) tract malignancy. It does not cause fever, weight loss, passage of blood by rectum, leukocytosis, or anemia. Those findings are red flags for organic disease and they demand investigation to detect or rule out a life-threatening condition.

Although symptoms typically begin during adolescence, most patients first seek treatment between the ages of 30 and 50. Onset is uncommon after age 65. Population-based surveys suggest that women patients with IBS outnumber men by a ratio of about 2:1, but the ratio among persons actually seeking treatment approaches 4:1.

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Some patients relate changes in the severity of their symptoms to dietary factors. A few report the onset of IBS after an episode of acute gastroenteritis. Many note an increase of symptoms at times of heightened emotional stress.

It has long been recognized that persons who fit diagnostic criteria for IBD are more likely than members of the general population to have psychiatric comorbidities. In fact, mood disorders (anxiety, depression) and somatoform disorders occur in more than 90% of patients with IBS. Moreover, the syndrome occurs in as many as 50% of patients with chronic fatigue syndrome, fibromyalgia, temporomandibular joint syndrome, and chronic pelvic pain. Only slightly less impressive are statistical associations between IBS and migraine headaches, endometriosis, and a history of sexual abuse in childhood.

For these reasons, the constellation of symptoms that we nowadays call irritable bowel syndrome was long regarded by physicians as purely psychosomatic, just another one of the many physical manifestations of unresolved emotional conflict that keep doctors busy and pay their office rent month after month. The absence of physical findings, the intermittency and elusiveness of symptoms, and the lack of clear-cut response to antispasmodics and other medicines that are effective in other bowel disorders have led to many psychiatric referrals and many prescriptions for psychoactive drugs.

The patient who is told that chronic, distressing, and perhaps disabling symptoms are due to "nerves" usually feels put down, humiliated, cheated. The physician with an appropriately scientific attitude can scarcely be satisfied with such a vague diagnostic formula as "spastic colon" for a condition that is without physical findings and that responds poorly to treatment, but is nonetheless seen day in and day out in primary care, internal medicine, and gynecology. And third party payers naturally object to doling out money for the diagnosis and treatment of a nebulous and relentlessly chronic disorder for which new treatments seem to be tried every few weeks, generally without much success.

All of these factors have provided strong motivation for the medical profession to characterize the disorder as precisely as possible, to determine whether it is one disease or several, and to uncover its cause or at least identify some associated physiologic or biochemical aberration.

A first step was to assume that a solitary clinical entity was masquerading under such varied names as nervous indigestion, spastic colon, intestinal neurosis, functional colitis, irritable colon, and mucous colitis, and to assign it a distinctive and apposite name.

In 1978 the British gastroenterologist Adrian Manning and his colleagues made an initial attempt to establish a clear diagnostic framework for what came to be called *irritable bowel syndrome*. The Manning criteria for the diagnosis of IBS are as follows:

- visible abdominal distention;
- relief of pain by bowel movement;
- increased frequency of stools with the onset of pain;
- looser stools with the onset of pain;
- rectal passage of mucus; and
- a sensation of incomplete evacuation.

Participants at the 13th International Congress of Gastroenterology, held in Rome in 1988, proposed significant modifications of the Manning criteria. The features of the disease that they identified as essential are now known as the Rome I criteria:

- abdominal pain that is relieved by defecation and that is associated with
- changes in the frequency or consistency of stools,
- bloating,
- nausea, and
- a sense of incomplete evacuation after passage of stool.

The Rome II criteria, published in 2000, are as follows:

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

- relieved by defecation;
- onset associated with a change in frequency of stools;
- onset associated with a change in the appearance of stools.

The Rome II formulation also recognizes the following symptoms as cumulatively supporting the diagnosis of IBS:

- abnormal stool frequency (more than three bowel movements per day or fewer than three bowel movements per week);
- abnormal stool form (lumpy/hard or loose/watery stool);
- abnormal stool passage (straining, urgency, or feeling of incomplete evacuation);
- passage of mucus;
- bloating or a feeling of abdominal distention.

The latest (but surely not the last) revision (2006) is known as the Rome III criteria:

Recurrent abdominal pain or discomfort and a marked change in bowel habits for at least six months, at least three days a month, and

At least two of the following:

- pain relieved by bowel movement;
- onset associated with a change in frequency of stools;
- onset associated with a change in appearance of stools.

It is understood in all of these diagnostic formulations that signs and symptoms of organic disease (fever, bleeding from the bowel, weight loss, nocturnal pain or diarrhea, evidence of infection or malignancy) are absent. In 1984, even before the development of the Rome I criteria, Kruis and associates proposed a scoring system incorporating negative values for a history of blood with stools and laboratory indicators of organic disease: elevated erythrocyte sedimentation rate (ESR), leukocytosis, anemia.

All sets of diagnostic criteria thus far established for IBS suffer from two fundamental defects. First, all positive diagnostic criteria are based on patient-reported symptoms, with the possible exception of physician-observed abdominal distention. Second, given the lack of any objective standard by which either to confirm or rule out the presence of IBS, attempts to validate any given set of diagnostic criteria lead inevitably to circular reasoning (A, therefore B; B, therefore A).

Repeated revisions of diagnostic criteria based on the assumption that IBS is a single disease with a unitary cause and on increasingly stringent analysis of statistics cannot reasonably be expected to clarify the essence of the condition, much less to lead directly to answers as to its etiology.

Efforts have been underway for several decades to correlate IBS with some demonstrable anatomic or biochemical deviation from normal or, failing that, at least to establish a plausible theory of its etiology. A major clue has been the close association between IBS and mood disorders and the fact that antidepressants are sometimes helpful in relieving the symptoms of IBS.

It has been postulated that complaints of bloating and a sense of inadequate emptying of the rectum may reflect an enhanced or distorted sensitivity to stretching or intraluminal pressure in the bowel due to altered processing of signals in the central nervous system (CNS).

Balloon distention studies of the ileum, sigmoid, and rectum have indeed shown that IBS patients experience pain or a sense of bloating at lower volumes than control subjects. In addition, limited studies have shown nonspecific differences on functional MRI and PET scans of the brain between IBS patients and others.

Some researchers have suggested that disturbances of bowel function (flatulence, constipation, diarrhea) may result from dysregulation of motility due to a local "lesion" in the bowel wall rather than, or in addition to, a central disorder. In this connection, particular attention has been focused on the monamine neurotransmitter serotonin (also called 5-hydroxytryptamine or 5-HT).

Disturbances in the production, transmission, and signaling functions of this substance in the CNS are directly involved in several forms of psychiatric illness, particularly clinical depression. Some antidepressants and antianxiety agents, and many drugs of abuse, produce their psychoactive effects by altering serotonin metabolism.

Serotonin is recognized not only as a central neurotransmitter but also as a peripheral signaling agent. It is one of several biological messengers that affect GI motility and secretion. In fact, 80-90% of the serotonin in the body is found in the walls of the digestive tract. A prominent symptom of carcinoid syndrome, which is due to excessive production of serotonin by neoplasms containing argentaffin cells, is chronic watery diarrhea. One study showed that intestinal biopsies from patients with constipation-predominant IBS secreted higher levels of serotonin in vitro.

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Seven types of serotonin receptor have been identified in peripheral nerves, blood vessels, and the GI tract. Digestive tract 5-HT_3 receptors are involved in nausea and vomiting, while 5-HT_4 receptors stimulate peristalsis. Some of the drugs currently used in the treatment of migraine and nausea act on peripheral 5-HT receptors.

The innervation of the digestive tract is derived from the autonomic nervous system, of which the parasympathetic division promotes muscle action (peristalsis) and the secretion of digestive fluids. Parasympathetic fibers reach the stomach, biliary tract, small intestine, and ascending colon as branches of the vagus (tenth cranial) nerve. The rest of the colon, including the rectum, receives its parasympathetic nerve supply from branches of the pelvic plexus, which arise in sacral segments of the spinal cord.

The alimentary tract is also supplied with sympathetic (adrenergic) nerve fibers, which originate in ganglia associated with thoracic and lumbar spinal segments. Sympathetic stimulation of digestive organs, which can be thought of as a feature of the body's "fight or flight" reaction to physical and emotional stresses, typically inhibits gastric and intestinal motility and suppresses the secretion or release of gastric and intestinal juices, bile, and pancreatic fluid.

Both divisions of the autonomic nervous system also contain afferent (sensory) fibers, which not only provide feedback to control centers in the brain stem and spinal cord but also mediate feelings of hunger or satiety, burning, bloating, and the urge to vomit or defecate.

Normal digestive function depends on a balance between parasympathetic and sympathetic stimulation, a fact reflected in the universal observation that anger, anxiety, grief, frustration, and other negative emotions can cause a wide spectrum of complaints referable to the digestive tract, including anorexia, nausea, heartburn, indigestion, belching, bloating, "butterflies," intestinal rumbling, and bowel irregularity.

The general cross-sectional anatomy of the GI tract is essentially the same from the esophagogastric junction to the rectum. From within outward, the gut wall consists of four

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more or less distinct layers: the mucosa or mucous membrane (several layers of secretory, absorptive, and supporting cells surrounding the lumen); the submucosa (a zone of connective tissue, blood vessels, and deeper glands); the muscularis (smooth muscle fibers divided into an inner circular layer and an outer longitudinal layer); and the serosa, a connective tissue sheath blending with surrounding structures.

In recent years it has been discovered that both layers of muscle in the walls of the alimentary canal are spirally disposed rather than strictly circular or longitudinal. This observation has led to a revision of nomenclature according to which the circular muscle layer is now called the *short pitch helicoidal layer* and the longitudinal layer is called the *long pitch helicoidal layer*. Their official names in *Terminologia Anatomica* are *stratum helicoidale brevis gradus* and *stratum helicoidale longi gradus*. I suspect that most of us will be on the other side of the turf before these terms catch on, if they ever do.

The coordinated action of the two muscle layers results in a mechanical churning action, which aids digestion of foods and absorption of nutrients, and in peristalsis, the wave-like activity by which the contents of the digestive tube are propelled forward.

Autonomic nerves supplying the digestive tract form an intricate network of unmyelinated fibers and nerve cell bodies distributed throughout its walls. These are divided into submucosal, myenteric, and subserosal plexuses.

The submucosal plexus (Meissner's plexus) provides innervation to secretory structures in the mucosa and submucosa. The myenteric plexus (Auerbach's plexus), situated between the longitudinal and circular muscle layers, promotes contraction chiefly of the circular layer. The subserosal plexus carries motor fibers to the longitudinal muscle layer. All three plexuses also carry afferent fibers for sensation and for feedback to regulatory systems.

For many decades, peptic ulcer disease was attributed to overproduction of stomach acid accompanied by a failure of biochemical or physiologic mechanisms that normally protect the gastric mucosa from attack by its own digestive secretions. The idea that psychological stress brings about this state through overstimulation of the vagus nerves was a dogma that few dared to question. Yet about 25 years ago Warren and Marshall in Australia presented irrefutable evidence that most cases of peptic ulceration of the stomach and duodenum result from infection by a gram-negative bacillus, *Helicobacter pylori*. Diagnostic procedures reliably identify the organism or its products in tissues, and its eradication by various antibiotic regimens predictably cures the disease.

The theory of an infectious cause for IBS has received some support from the fact that a significant subset of patients report that their symptoms began after an episode of acute gastroenteritis. Although treatment of IBS with various antibiotics, including rifaximin, has led to a marked reduction of symptoms in some patients, there is presently insufficient evidence for an infectious cause.

Because infestation with certain unicellular intestinal parasites (*Blastocystis, Dientamoeba, Giardia*) causes symptoms closely resembling those of IBS, some have concluded that one or more of these are causative agents of the disease. This is one of several areas in which the lack of an objective diagnostic standard for IBS continues to foster muddy thinking and conclusions of highly dubious validity.

It has been suggested that the overgrowth of certain bacteria in the small intestine may induce immune-mediated damage to neurons in the myenteric plexus. In 2002 a group of Swedish researchers performed jejunal biopsies on a small series of patients with severe IBS. They reported finding degenerative changes and signs of low-grade chronic inflammation in the myenteric plexuses of most of their subjects, but no such changes in specimens from persons without IBS. The finding of increased levels of cytokines (interleukin 1, interleukin 6, tumor necrosis factor) in blood and rectal biopsy specimens from IBS patients lends further support to the concept of an immune cause.

Whatever value rigorously applied diagnostic criteria may have in research, they have little to offer in clinical practice. When typical symptoms have been occurring intermittently for months or years, their mere recitation by the patient virtually establishes the diagnosis of IBS.

A review of systems and careful physical examination are nonetheless necessary to rule out other conditions. The differential diagnosis includes inflammatory bowel disease (Crohn's disease, ulcerative colitis), celiac disease, lactose intolerance, and infestation with protozoan parasites, especially *Giardia lamblia*.

Recommended laboratory studies include blood tests to detect anemia, leukocytosis, or elevated ESR. Celiac disease is a chronic allergic response to gliadin, a protein found in glutens (certain cereal grains, including wheat and corn). Symptoms vary widely but can mimic diarrhea-predominant IBS. The American College of Gastroenterology accordingly recommends that all patients with symptoms of IBS be tested for celiac disease. Testing for thyroid disease, lactose intolerance, and intestinal parasitism have also been advised.

Routine endoscopy, rectal biopsy, and abdominal ultrasound examination or other imaging studies are not recommended. For the patient with severe anxiety about malignancy, however, some of these studies may have therapeutic value.

More aggressive diagnostic assessment is appropriate in any patient who first develops symptoms after age 50, who has a marker of organic disease such as weight loss or blood in the stool, or who has a family history of inflammatory bowel disease or gastrointestinal malignancy.

The treatment of IBS starts with the development of a comfortable relationship between the patient and the primary care physician or specialist. The physician must be willing to spend as much time as necessary in educating the patient, clarifying the benign but chronic nature of the disease, and securing the patient's collaboration in what may be a long-term therapeutic process. The patient needs to understand that there is presently no cure for IBS and that no available medicines control symptoms perfectly.

The management of the disease must be individualized on the basis of the patient's symptoms, including the severity of pain and disablement and the perceived effects of diet, stress, and other factors. Some patients note that pain, bloating, and bowel dysfunction are aggravated by alcohol, caffeine, chocolate, carbonated beverages, fatty foods, fructose, sorbitol, or lactose. Prescription medicines, particularly antibiotics, hormones (oral contraceptives, estrogen replacement therapy), and benzodiazepine tranquilizers and hypnotics, may also worsen symptoms.

Although true food allergy has not been demonstrated in IBS, exclusion of milk, wheat, or eggs from the diet has been helpful for some. The addition of fiber (wheat bran, corn fiber, ispaghula husk) to the diet and the use of bulking agents (psyllium, calcium polycarbophil) may improve constipation in IBS, but pain relief with these agents is minimal, and they often increase bloating. Patients with constipation-predominant IBS are advised to increase their water intake. Reducing the volume of meals and eating more slowly may improve bloating.

Changes in lifestyle may be advisable in order to avoid extreme psychological stressors. Limited studies have shown that some patients improve with relaxation therapy, cognitive-behavioral therapy, hypnosis, or biofeedback. Treatment with tricyclic antidepressants (TCAs) or selective serotonin reuptake inhibitors (SSRIs) has reduced abdominal pain and improved the quality of life for some patients, but the effects of these agents are modest and unpredictable. TCAs have performed better in diarrhea-predominant disease.

Although anticholinergic (atropine-like) drugs have been routinely prescribed for IBS symptoms for more than a century, they show no consistent results and often aggravate constipation. In addition, they can have troubling side effects (dry mouth, blurred vision, urinary retention). Mebeverine, which acts directly on the smooth muscle of the GI tract rather than through parasympathetic blockade, relieves cramping and bloating for many patients without causing anticholinergic side effects.

Laxatives and stool softeners can improve bowel function in constipation-predominant IBS but have little impact on the total clinical picture. Because IBS is relentlessly chronic, patients who use laxatives of the stimulant type risk becoming habituated to increasingly potent agents. The prostaglandin E1 derivative lubiprostone and osmotic agents such as polyethylene glycol, sorbitol, and lactulose, which do not directly promote bowel action or lead to drug tolerance, are preferred in IBS.

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Antimotility agents such as loperamide can control diarrhea temporarily but do not relieve pain and can worsen gas entrapment or bring on constipation and even paralytic ileus (obstruction due to atony of smooth muscle fibers in the bowel wall).

As with most problems for which scientific medicine has provided only incomplete or unsatisfactory answers, nonprescription herbal remedies have often been promoted for IBS. Some sufferers have apparently obtained significant relief from preparations containing guar gum, peppermint oil, chamomile, lemon balm, angelica, or some combinations of these, but controlled studies are lacking.

Probiotic therapy of IBS with yogurt has recently received considerable media attention. The term *probiotic* refers to the introduction of live microorganisms into the human digestive tract to achieve a health benefit or to mitigate a disease process.

Yogurt is a dairy food produced by the controlled bacterial fermentation of milk sugar (lactose) to lactic acid. The acid yields a pleasant degree of sourness, denatures milk protein (lactalbumin) to form a soft curd, and inhibits bacterial overgrowth and spoilage.

Yogurt and similar soft-curd dairy products have been dietary staples in eastern Europe and Asia for thousands of years. Milk stored in goatskin bags ferments under the influence of bacteria (*Lactobacillus bulgaricus, Streptococcus thermophilus*, and others) that are naturally present. A new batch of yogurt can be started by inoculating fresh milk with a small amount of a previous batch.

Early in the twentieth century the Russian biologist Elie Metchnikoff, who received a Nobel Prize for his studies on phagocytosis, promoted dietary yogurt as a means of prolonging life. Yogurt is essentially a culture of living nonpathogenic microorganisms. Its introduction into the diet can lead to a change in intestinal flora, with a predominance of *Lactobacillus*. Although Metchnikoff could not explain how this was supposed to improve health, and could offer no more

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compelling support for his theory than the long life spans of Bulgarian peasants, his enthusiasm won over many adherents to his cause throughout Europe.

In the 1950s and 1960s yogurt began to be promoted in this country as a health food. A variety of products appeared on the market, including yogurts whose natural sourness was tempered by the addition of fruit or jam, and whose texture was modified with pectin, gelatin, and emulsifiers. Some persons with mild lactose intolerance found that they could eat yogurt without ill effects, because most of its lactose had been chemically converted to lactic acid.

The effect of yogurt on the intestinal microflora was exploited when it was found that it could reverse some cases of antibiotic-associated diarrhea, in which benign bacteria had been eradicated from the bowel by broad-spectrum antibiotic treatment. Although also promoted as a means of preventing or treating vulvovaginal candidosis, yogurt has performed poorly in clinical trials for this indication.

Regular consumption of yogurt has been shown in several studies to decrease pain and bloating associated with IBS and to reduce intestinal transit time, thus relieving diarrhea. In controlled trials, yogurts containing cultures of *Bifidobacterium lactis* DN-173 010 or *B. infantis* 35624 have clearly outperformed others.

In one small study of adult women with IBS, those who ate yogurt containing *Bifidobacterium* daily during a four-week period experienced a significant reduction not only in pain but also in postprandial abdominal distention as measured with a tape, when compared with control subjects who ate a non-fermented dairy product.

Although Activia, a popular brand of yogurt containing both *Lactobacillus* and *Bifidobacterium*, has been conspicuously effective for many IBS patients, no form of yogurt yields uniformly predictable results. Patients who experience an increase rather than a decrease in symptoms with yogurt may be displaying extreme sensitivity to traces of lactose or an allergic reaction to milk protein. Once again, the impossibility of isolating or classifying patients with "true" IBS robs clinical trials of scientific rigor and renders their outcomes questionable.

To conclude on a more positive and hopeful note, two drugs developed during the past decade to alter serotonin metabolism have shown remarkable efficacy and specificity in some patients with IBS.

In women with diarrhea-predominant IBS, the 5-HT_3 receptor antagonist alosetron (Lotronex) lessens abdominal pain, reduces stool frequency and defecatory urgency, and improves stool consistency. The usefulness of this agent is limited by the risk of severe constipation and ischemic colitis, a potentially serious inflammatory process due to focal impairment of blood supply to the colon, which causes edema, hemorrhage, and sometimes ulceration and necrosis.

Alosetron was withdrawn from the U.S. market in 2000 because of these hazards, but reinstated in 2002 in response to a strong public outcry. It is presently marketed at a lower dose, and is available only for patients who have failed conventional treatment and who are enrolled in a risk management program. The drug is contraindicated in constipation-predominant and mixed IBS. Alosetron is generally ineffective in men.

Tegaserod (Zelnorm), which is classified as a 5-HT_4 receptor agonist, normalizes bowel function and yields global relief of symptoms in some women with constipation-predominant IBS. In treatment-responsive patients, administration of tegaserod has been associated with an improvement in work attendance and productivity, enhanced quality of life, and reduced utilization of health care resources. Like alosetron, tegaserod is generally ineffective in men.

Tegaserod can cause diarrhea and, like alosetron, may occasionally precipitate ischemic colitis. In addition, its use has been associated with an unacceptably high risk of serious cardiovascular disease. In 2007 the drug was temporarily withdrawn from the market. It was again made available later that year, but only to patients who have failed other therapies. Tegaserod is currently not approved for use in the countries belonging to the European Union.

Cilansetron, a 5-HT_3 antagonist that has been found effective in diarrhea-predominant IBS in both sexes, is currently in regulatory limbo because of safety issues. It seems likely that, within the next five to ten years, pharmaceutical research will develop safer agents that are effective for the treatment of both types of IBS in both men and women.

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