

Management of the Irritable Bowel Syndrome

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Irritable bowel syndrome (IBS) is the most common disorder diagnosed by gastroenterologists and one of the more common ones encountered in general practice. The overall prevalence rate is similar (approximately 10%) in most industrialized countries; the illness has a large economic impact on health care use and indirect costs, chiefly through absenteeism. IBS is a biopsychosocial disorder in which 3 major mechanisms interact: psychosocial factors, altered motility, and/or heightened sensory function of the intestine. Subtle inflammatory changes suggest a role for inflammation, especially after infectious enteritis, but this has not yet resulted in changes in the approach to patient treatment. Treatment of patients is based on positive diagnosis of the symptom complex, limited exclusion of underlying organic disease, and institution of a therapeutic trial. If patient symptoms are intractable, further investigations are needed to exclude specific motility or other disorders. Symptoms fluctuate over time; treatment is often restricted to times when patients experience symptoms. Symptomatic treatment includes supplementing fiber to achieve a total intake of up to 30 g in those with constipation, those taking loperamide or other opioids for diarrhea, and those taking low-dose antidepressants or infrequently using antispasmodics for pain. Older conventional therapies do not address pain in IBS. Behavioral psychotherapy and hypnotherapy are also being evaluated. Novel approaches include alosetron; a 5-HT₃ antagonist, tegaserod, a partial 5-HT₄ agonist, κ -opioid agonists, and neurokinin antagonists to address the remaining challenging symptoms of pain, constipation, and bloating. Understanding the brain-gut axis is key to the eventual development of effective therapies for IBS.

In this article on the management of irritable bowel syndrome (IBS), the focus is on (1) the definitions, epidemiology, and pathophysiology as a means of understanding strategies for optimal management; (2) the natural history and “safety” of the disorder that justifies a conservative and reassuring approach to patients; and (3) consideration of older (conventional) and newer treatments of IBS.

IBS Overview: Definitions, Epidemiology, Pathophysiology

Irritable bowel syndrome (IBS) is defined as “a functional bowel disorder in which abdominal pain is associated with defecation or a change in bowel habit, with features of disordered defecation and distention.”¹ The consensus definition and criteria for IBS have been formalized in the “Rome criteria,” which are based on Manning criteria (Table 1). The Rome criteria have come to be accepted as the state-of-the-art criteria for research studies; they have recently been refined and simplified for IBS to focus on the essential elements of abdominal pain and alteration of bowel habits.¹ However, validation of these criteria has been hampered by the lack of any biologic marker for IBS. The specificity of the symptoms alone is relatively poor. Specificity is enhanced by the inclusion of limited tests to exclude organic disease.^{2,3} Thus, IBS is a disorder that can be diagnosed positively on the basis of a series of symptom criteria⁴⁻⁶ and limited evaluation to exclude organic disease.⁷⁻⁹

The prevalence data¹⁰⁻¹² from questionnaire studies range from the 2.9% estimate from 6 U.S. surveys of the prevalence of the diagnosis of IBS¹³ to the prevalence of symptoms in a random sample of the population, which may reach up to 20% depending on the criteria used.¹⁰⁻¹² The precise incidence of IBS is unclear, but it has been estimated at almost 1% per year.¹⁴

Symptom subgroups based on the predominant bowel habit (i.e., constipation-predominant IBS, diarrhea-predominant IBS, and IBS with alternating bowel movements) have equal prevalence rates (5.2 per 100) in epidemiologic studies in Olmsted County, Minnesota,¹¹ although clinical samples show a different distribution, possibly reflecting regional research expertise or interest. The gender ratio in these subgroups is similar except in constipation-predominant IBS, which is more common in women.¹¹ The female preponderance is more apparent

Abbreviations used in this paper: IBS, irritable bowel syndrome; SSRI, selective serotonin reuptake inhibitor.

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Table 1. Criteria for IBS

Manning criteria ⁴
Pain relieved by defecation
More frequent stools at the onset of pain
Looser stools at the onset of pain
Visible abdominal distention
Passage of mucus
Sensation of incomplete evacuation
Rome II criteria ¹
At least 12 weeks or more, which need not be consecutive, in the previous 12 months of abdominal pain or discomfort that has 2 of 3 features:
Relief with defecation
Onset associated with a change in the frequency of stool
Onset associated with a change in form (appearance) of stool

Data from Manning et al.⁴ and Drossman et al.¹

in clinical samples (3–4:1) than in those with symptoms who did not seek medical attention (less than 2:1) and were identified by mailed questionnaires.¹⁴ In the U.S. householder study, 11.6% had IBS, 3.6% had functional constipation, and 1.8% had functional diarrhea.¹⁰ The prevalence of IBS is lower in the elderly.¹⁵ In Olmsted County, Minnesota, the prevalence of IBS among people aged 65–93 years was 10.9%, compared with 17% in those aged 30–64 years.¹¹ Traditionally, IBS is not diagnosed in those patients presenting with the symptom complex for the first time after the age of 60 years.¹⁶

IBS Variants Unrecognized by the Rome II Criteria

Although the Rome II criteria for IBS are quite robust, they are still not comprehensive and do not encompass some clinical patterns of IBS that are recognized by clinicians and are amenable to newer therapies. First, these criteria exclude subgroups based on predominant bowel dysfunction.

Second, the criteria do not address the postprandial exacerbation of symptoms. Symptom-based and experimental studies, typically in relatively small samples of patients, suggest that postprandial symptoms and dysfunctions may be important, but this feature has not yet been included in Rome II IBS criteria. Urgency and abdominal pain or diarrhea are frequently encountered in the postprandial period, and a subgroup of patients has a prominent tonic and phasic response to feeding.¹⁷ This can be assessed by specific questions in the clinic and has clear physiologic correlates (increased postprandial propagated contractions in diarrhea-predominant IBS^{17,18} or reduction of colonic contractions in constipation-predominant IBS¹⁷), objectively shown by colonic manometry.^{17,18} Recent studies confirm the association with food “sensitivity” or “intolerance,” which may merely

reflect exacerbation of symptoms by food.^{19,20} In fact, patients with diarrhea-predominant IBS have higher serotonergic responses to a standard meal, suggesting that serotonin might mediate these symptoms.²¹ Ragnarsson and Bodemar²² found that almost 50% of patients with IBS reported worsening of pain postprandially. Other studies with thorough documentation of meal-related symptoms will be needed in the future.

Third, the Rome II criteria do not encompass patients in whom functional, painless diarrhea may be associated with postprandial urgency, borborygmi, and a sense of incomplete rectal evacuation.¹⁶ Because of the absence of abdominal pain, these patients would not be considered to have IBS on the basis of the Rome II criteria, contrary to the experience and practice of many clinicians, as documented in the literature almost 40 years ago.¹⁶

Impact of IBS

It is estimated that only 10%–25% of patients with IBS seek medical care; however, the illness has an enormous economic impact. In the United States alone, the economic impact is estimated at \$25 billion annually (Table 2) through direct costs of health care use and indirect costs of absenteeism from work.^{10,23–26} In countries with socialized medicine, direct charges are lower,^{27–30} but this expenditure may still account for 0.5% of health care budgets.²⁴

Patients with IBS undergo more surgical procedures, including hysterectomy, cystoscopy, and appendectomy.^{31,32} IBS accounts for 2.4–3.5 million physician visits in the United States annually,³³ making it the most common diagnosis in gastroenterologists’ practice (approximately 28% of all patients) and accounting for 12% of primary care visits. Annually, there are 2.2 million medication prescriptions for IBS patients in the United States.³⁴ Patients with IBS have 3 times more absenteeism from work and report reduced quality of life.¹⁰

Table 2. Epidemiology and Cost Statistics of IBS

Prevalence of IBS varies between 5% and 25%
Similar prevalence in several countries and ethnic groups (e.g., black, hispanic, and white U.S. population)
Constipation-predominant IBS is more common in women
Female predominance (3–4 F:1 M) in those seeking health care; approximately equal M:F ratio among community nonpresenters with IBS symptoms identified by surveys (except constipation IBS, in which F > M)
10%–25% of IBS patients seek medical care
IBS accounts for 2.4–3.5 million physician visits and 2.2 million medication prescriptions in the United States annually
3-Fold absenteeism from work in IBS, roughly equivalent to the common cold
Annual resource impact of IBS in the United States estimated at \$25 billion; two thirds for indirect costs

Data reviewed by Camilleri and Williams.²⁵

Overview of Mechanisms as a Basis for Therapy

Symptoms in IBS have a physiologic basis, but there is no single physiologic mechanism responsible for symptoms of IBS. Table 3 summarizes the pathophysiologic mechanisms that appear to contribute to IBS. These individual mechanisms are not mutually exclusive. IBS is considered a biopsychosocial disorder resulting from a combination of 3 interacting mechanisms: psychosocial factors, altered motility (Table 4^{35–47}) and transit, which may reflect severity of bowel dysfunction,^{48–50} and increased sensitivity (Table 5^{51–56}) of the intestine or colon. Preliminary data suggest a genetic contribution to functional bowel disorders⁵⁷ that requires further validation. Gastrointestinal hypersensitivity and anorectal dysfunction have been extensively studied and are so frequently associated with the syndrome^{51–55} that they are reasonable targets for therapy. It has been hypothesized that altered peripheral functioning of visceral afferents (recruitment of silent nociceptors, increased excitability of dorsal horn neurons) and the central processing of afferent information are important in the altered somatovisceral sensation and motor dysfunction in patients with functional bowel disease.⁵⁷ Vagal nerve dysfunction and abnormal sympathetic adrenergic function have been demonstrated in subgroups of patients with constipation- and diarrhea-predominant IBS, respectively.^{58,59}

Recently, much attention has been focused on possible persisting neuroimmune interactions after infectious gastroenteritis, which might result in continuing sensorimotor dysfunction.⁶⁰ However, the role of infection in IBS is still controversial. Infectious diarrhea precedes the onset of IBS symptoms in 7%–30% of patients in dif-

Table 3. Pathophysiology of IBS

A biopsychosocial disorder
Altered motility and enhanced visceral perception
~50% of IBS patients have psychologic symptoms at the time of presentation
The role of physical and sexual abuse in the development of IBS is controversial
Up to one third (range, 7%–31%) of IBS presenters recall an antecedent gastroenteritis
Proposed mechanisms contributing to IBS ^a
Abnormal motility
Heightened visceral perception: peripheral or central
Psychologic distress
Intraluminal factors irritating small bowel or colon
Lactose, other sugars
Bile acids, short-chain fatty acids
Food allergens
Postinfectious neuroimmune modulation of gut functions

^aInteraction between different mechanisms may occur in individual patients.

Table 4. Alterations in Bowel Motility in IBS

Psychologic ³⁵ and physical ³⁶ stress increase colonic contractions in experimental studies modeling IBS
Diarrhea-predominant IBS
Prominent colonic response to feeding: increased postprandial colonic contractions ¹⁸
Fast colonic and propagated contractions increased with diarrhea and decreased in constipation-predominant IBS ^{18,37}
Accelerated whole-gut transit ³⁸ ; faster ascending and transverse colon emptying ³⁹ is positively correlated with stool weight
Constipation-predominant IBS
Decreased number of fast colonic and propagated contractions in constipation-predominant IBS ^{18,37}
Idiopathic constipation and normal anorectal and pelvic floor function: delay in whole-gut transit, and rate of ascending and transverse colon emptying ⁴⁰
Rectal and colonic compliance and tone are normal, although few reports suggest minor abnormalities in constipation of unclear clinical significance ^{41–43}
Pain-predominant IBS
“Clustered” contractions in the jejunum and ileal propagated giant contractions during episodes of abdominal colic ⁴⁴ are not pathognomonic for IBS ^{45,46}
Sensory abnormalities accompany postprandial motor dysfunctions ⁴⁷

ferent series.^{16,60–63} Certain toxins seem more likely to be associated with long-term symptoms in patients with prior *Campylobacter* enteritis. It is not clear whether a previous infectious episode could induce a physiologic response, causing persistent symptoms, even in the absence of residual demonstrable inflammation of the gut. Some have hypothesized that microscopic inflammatory changes such as infiltration of the enteric nervous system contribute to the development of IBS. Gwee et al.⁶⁰ have shown that about a quarter of patients with infectious diarrhea IBS continue to experience symptoms after 3 months. However, these patients were admitted to their local hospital, suggesting they suffered a severe form of diarrhea, raising questions about the generalizability of the observation. In fact, the community diarrhea-based study in Nottingham, England, suggests that fewer than 10% of patients with acute diarrhea went on to develop

Table 5. Enhanced Visceral Perception in IBS

Diarrhea-predominant IBS
Lower thresholds for sensation of gas, stool, discomfort, and urgency by progressive rectal balloon distention, accompanied by excessive reflex contractile activity in the rectum ^{51,52}
Constipation-predominant IBS
Discomfort at greater distention volumes (reduced sensitivity ⁵²) than in health; others report rectal or sigmoid hypersensitivity ⁵⁵
Normal or increased thresholds for somatic pain stimuli ⁵⁶
Pain-predominant IBS
Increased visceral perception on rectosigmoid, ileal, and anorectal balloon distention ^{44,51–55}
Normal bowel compliance

IBS. From the study of Gwee et al.,⁶⁰ it appears that the “mind” plays a greater role than “matter” because life event stress and hypochondriasis are predictive factors in the persistence of IBS.⁶⁴ In contrast, physiologic parameters such as whole-gut transit time and sensory thresholds are not different in patients with and without IBS symptoms 3 months after an episode of “infectious” diarrhea.

Some patients with IBS also have carbohydrate intolerance, which may contribute to the symptoms of IBS; intolerance of sugars is partly determined by the ethnicity of the patient. Thus, lactose intolerance has a higher prevalence among Hispanic and black patients, whereas fructose and sorbitol intolerance are more prevalent among people of Northern European extraction.⁶⁵ The clinical effects of lactose intolerance are also dependent on the total carbohydrate load because exposure to the equivalent of an 8-ounce glass of milk per day does not seem to cause symptoms.⁶⁶ Gas formation as a result of maldigestion in the small intestine and subsequent metabolism in the colon accounts for bloating⁶⁷; formation of osmotically active metabolites leads to diarrhea. Measurements of intestinal gas have not always correlated with symptoms.⁶⁸

Experimental data suggest that food allergens may also be important in IBS.⁶⁹ One clinical trial showed that symptoms in 40% of patients with IBS persistently improved with dietary exclusions.⁷⁰ The role of dietary exclusion is still controversial, although there is evidence that the greater rate (although not the quantity) of gas excretion in IBS patients can be reduced by exclusion diets, and this change parallels improvement in symptoms.⁷¹

The ileum of patients with IBS is excessively sensitive to the secretory effects of perfused bile acids.⁷² Recent studies also emphasize the interaction between gas retention and other cofactors, particularly in patients with constipation-predominant IBS. This led to the experimental use of colonic prokinetics as a means of enhancing gas clearance,^{73–75} which showed that gas clearance was increased. However, this was associated with exacerbation of abdominal pain, a well-known side effect of the anticholinesterase neostigmine, and other approaches that do not increase pain are needed.

Stress and emotions affect gastrointestinal function⁷⁶ and cause symptoms to a greater degree in IBS patients than in healthy controls. Psychologic symptoms that are more common in patients with IBS include somatization, anxiety, hostility, phobia, and paranoia.^{77–79} Identification of this comorbidity and somatization are key to optimizing patient treatment.⁸⁰ Patients with IBS seen

in medical clinics have elevated scales of depression, anxiety, somatization, and neuroticism.^{81,82} At the time of presentation, almost half of the IBS patients have one or more of these symptoms. Because psychosocial symptoms modulate experience of somatic symptoms, they contribute to the greater illness behavior, increased physician consultations, and reduced coping capability that are so common among IBS patients. Life event stressors and hypochondriasis are important determinants of patients with postinfectious diarrhea who develop the full picture of IBS at 3 months.

The role of physical and sexual abuse in the development of the psychosocial factors manifested by patients with functional gastrointestinal disease is controversial.^{83,84} If identified, abuse requires specific and expert care.

Thus, other therapies focus on the psychotherapeutic angle.⁸⁵ Until relatively recently, attempts to develop effective therapies were hampered by poor trial design.⁸⁶ The psychopathology or psychologic distress manifested particularly in patients presenting to the clinic⁸⁷ and in those with a history of abuse⁸⁸ emphasize the importance of the holistic approach to the patient.

Natural History of IBS: A “Safe Diagnosis” and the Importance of Reassurance

IBS is a chronic disease whose course is extremely variable in the general population. Although functional gastrointestinal symptoms are common in middle-aged persons, the overall prevalence in a community sample seems relatively stable over 12–20 months. There is a substantial degree of “turnover” because many people’s symptoms fluctuate over time, and they therefore move in and out of the IBS cohort.^{11,89} IBS is a “safe” diagnosis. Patients followed up with such a diagnosis seldom turn out to suffer from serious organic disease, and the time-honored clinical strategy to reassure the patient that the diagnosis is benign without significant risk of missing an organic disease is well justified.^{90,91}

Fluctuation of symptoms often results in seeking of further health care. Repetitive investigations serve merely to reinforce the illness behavior. On the other hand, it is equally important that physicians not attribute to IBS those symptoms that do not fit the usual syndrome in the individual patient or symptoms that do not conform with the broader characteristics of the symptom complex embodied in the Manning or Rome criteria. The development of rectal bleeding, anemia, and a high erythrocyte sedimentation rate were significant negative predictive factors for IBS in the study of Kruis et

al.² of IBS and constitute alarm features that are easy to elicit in the evaluation of IBS patients presenting with gastrointestinal symptoms. Similarly, in the presence of rectal bleeding (which was not an independent significant predictor in the study of Kruis et al.), further investigation is mandatory.

Diagnostic Strategy in IBS Patients

General Principles

The diagnosis of IBS is based on the identification of symptoms consistent with the syndrome and the exclusion of organic diseases that have similar clinical presentations.¹⁻⁸ A conservative management approach includes identification through symptom-based criteria (e.g., Manning⁴ or Rome II¹ criteria) and therapeutic trials. There are now relatively inexpensive diagnostic tests that aid in identification of the underlying mechanism (Figure 1) in patients who do not respond to empiric trials; by definition, tests should follow the empiric trial in this relatively benign syndrome. Recent reviews, endorsed by the Practice Committee of the American Gastroenterological Association,⁸ have suggested strategies for diagnosis and management of IBS.

The first step is a careful assessment of the patient's symptoms. Manning or Rome criteria can be used in a proactive, positive manner to raise the clinical suspicion of IBS. The absence of rectal bleeding is helpful in excluding organic disease. A thorough physical examination and a limited series of initial investigations are needed to exclude organic structural, metabolic, or infectious diseases.⁴⁻⁷ These include hematology and chemistry tests; erythrocyte sedimentation rate; stool examination for occult blood, ova, and parasites (in those with diarrhea predominance); flexible sigmoidoscopy; and, in those over 40 years of age or with a family history of colon polyps or cancer, a complete colonic evaluation.

Formal studies have assessed the role of a more specialized investigation. Ultrasonography or computed tomography of the abdomen and pelvis^{31,92,93} and rectal biopsy⁹⁴ provide little incremental value to the simpler work-up proposed for IBS. However, rectal biopsy may be appropriate to exclude lymphocytic/microscopic or collagenous colitis in some patients with painless diarrhea. The controversy of flexible sigmoidoscopy versus colonoscopy as a screening test for organic disease is still unresolved; one approach is to use American Cancer Society or World Health Organization criteria⁹⁵⁻⁹⁷ to select the endoscopic procedure dictated for screening for colon cancer in patients with suspected IBS.

A careful search for psychosocial factors, stress, and possibly physical and sexual abuse will identify issues that may require specific attention. Establishing an effective physician-patient relationship and sizing up the patient's agenda are crucial to effective treatment of the patient.⁸⁸ Figure 1 summarizes the approach to patient care in patients with IBS.

Pelvic floor dysfunction is a discrete disorder and may present with symptoms consistent with constipation-predominant IBS: constipation, sense of incomplete evacuation, and secondary abdominal pain. These symptoms result from failed coordination of functions that normally result in rectal evacuation. A careful history, physical examination, and simple clinical or radiologic tests can identify these patients, and biofeedback/physical relaxation leads to significant improvement, even cure; no pharmacologic or surgical therapy is useful in this condition. Proper identification and treatment of pelvic floor dysfunction is a key to at least partial relief in patients with coexisting constipation-predominant IBS.⁹⁸

A careful review of the results of the screening tests helps reassure the patient. If any of the test results are

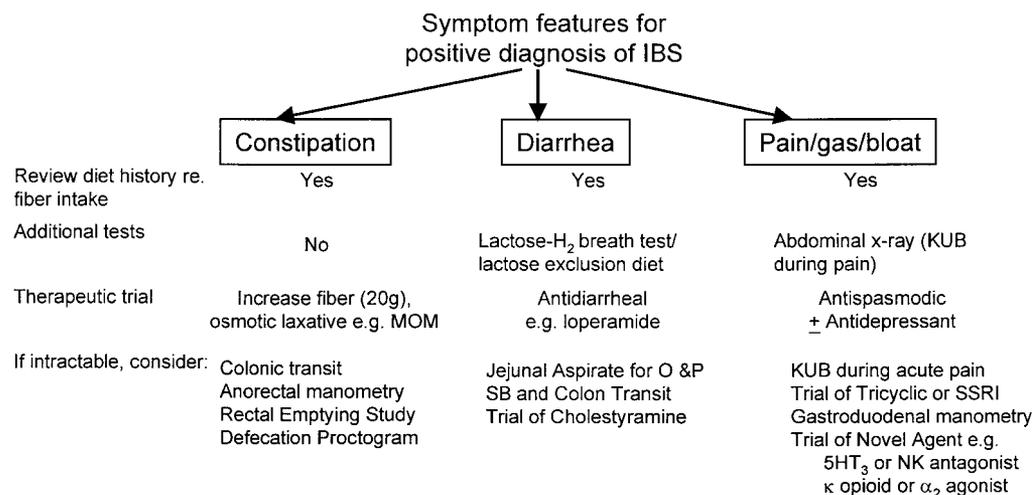


Figure 1. Algorithm for initial management of patients with IBS according to predominant symptoms. If symptoms fail to respond to initial treatment, further investigations are required. Data from Camilleri et al.⁷

Table 6. Initial Treatment: The Therapeutic Trial

Reassurance and an effective doctor–patient relationship	
Diarrhea	Antidiarrheal agents such as diphenoxylate or loperamide (e.g., 2 mg as needed, up to 4/day)
Diarrhea and pain	Alosetron (1 mg 2× daily) approved for women with IBS pain and diarrhea
	Tricyclic antidepressants, such as desipramine, 50 mg 3× daily, or amitriptyline, 10–25 mg 2× daily, significantly relieve diarrhea and associated pain
Constipation	Dietary fiber supplementation (20 g/day)
	Osmotic laxatives such as a magnesium salt, lactulose, or polyethylene glycol are usually efficacious
Pain	Antispasmodics for pain on an as-needed basis; effectiveness unclear

abnormal, further specific investigation or treatment may be necessary. When organic structural or biochemical disorders are excluded, it is useful to reassure the patient of the significance of these normal findings.

A therapeutic trial is part of the diagnostic process (Table 6). Typically, a therapeutic trial should be pursued for at least 4 weeks. There is also evidence that one of the medications in a therapeutic class may be more effective in an individual, and there may be some advantage to sequential trials of different drugs in the same group. This is particularly relevant in trials of antidepressants, as demonstrated by Clouse et al.⁹⁹ This clinical observation reflects partly the repetitive response to placebo in IBS. Alternatively, it may reflect the different pharmacologic effects (serotonergic, adrenergic, anticholinergic) of the different antidepressant drugs and the possibility that specific neurochemical modulation may be necessary in different patients. Suggested approaches to the use of therapeutic trials in different patient subgroups are summarized in Table 6.

Additional diagnostic tests (Figure 1) may be required if the therapeutic trial fails.⁸ The most appropriate test will depend on the predominant symptom in the individual patient and the previous therapeutic trials undertaken. In patients with predominant constipation, colonic transit and tests of the stool evacuation process are indicated when a trial of fiber and osmotic laxatives fails. In patients with predominant diarrhea or pain-gas-bloat symptoms, a more detailed dietary history may identify factors that may be aggravating or even causing those symptoms. Among patients with predominant diarrhea, lactose, fructose, or sorbitol intake may induce this symptom. Therefore, a lactose-hydrogen breath test should be performed, or a lactose-exclusion diet should be included in the therapeutic trial. Among patients

with predominant pain-gas-bloat, a plain abdominal radiograph during an acute episode of pain provides some reassurance that there is no mechanical obstruction. Thereafter, a therapeutic trial with a smooth muscle relaxant (discussed below) is reasonable. The effectiveness of smooth muscle relaxants in the treatment of IBS is controversial.

Conventional Therapies for IBS

Effective management requires an effective physician–patient relationship⁸⁸ and attention to the art of healing in addition to the science of modern medicine. Education of physicians, surgeons, gynecologists, and patients regarding IBS and its management is essential to reduce direct costs; new insights in pathophysiology and mechanisms, novel pharmacotherapy (Table 7), and teaching patient skills to manage the syndrome are likely to reduce indirect or societal costs and may have an impact on intangible costs.²⁵

Role of Fiber in Treatment of IBS

In patients with constipation-predominant IBS, fiber accelerates colonic or oroanal transit¹⁰⁰; this acceleration is associated with increased stool weight and percentage of unformed stools. As a group, patients with constipation-predominant IBS do not consume less dietary fiber than control subjects.¹⁰¹ It is often postulated that fiber may decrease intracolonic pressure and thereby

Table 7. Novel IBS Therapy Based on Pathophysiology and Pharmacodynamics

Diarrhea	5-HT ₃ antagonists (e.g., alosetron): retard small bowel and colonic transit
	Anticholinergics, selective M3 type: antispasmodic with antidiarrheal potential
	CCK antagonist: loxiglumide does not inhibit colonic response to food ingestion in humans
Constipation	5-HT ₄ agonists (e.g., tegaserod and prucalopride): accelerate small bowel and colonic transit
Pain	α ₂ -Adrenergic agonist (e.g., clonidine): reduces tone, increases compliance, decreases pain sensation during distention in health
	κ-Opioid agonist (e.g., fedotozine): increases threshold for distention-induced pain in IBS
5-HT	5-HT ₁ agonist: relaxes colonic tone, reduces sensation
	5-HT ₃ antagonist: reduces colonic tonic response to feeding, colonic compliance, and sensation of volume distentions
	5-HT ₄ antagonist: ? inhibits colonic sensation in experimental models
Neurokinin antagonists:	reduce visceral sensation; motor actions in colon depend on receptor subtype in experimental models

reduce pain because it is recognized that wall tension is one of the factors that contributes to visceral pain.^{102–104} Fiber reduces bile salt concentrations in the colon, and it has been speculated that this indirectly reduces colonic contractile activity.¹⁰⁵ However, symptom relief was not associated with changes in rectosigmoid motility.¹⁰⁶

Fiber alleviates pain in children with idiopathic chronic abdominal pain.¹⁰⁷ However, the mechanism of this beneficial effect is unclear, and any perceived benefit may be secondary to the relief of constipation. When formally tested, fiber supplementation did not reduce phasic contractile activity in IBS patients,¹⁰⁶ and the effects of fiber supplementation on colonic tone, sensation, and compliance in IBS have not been evaluated adequately. There have been few randomized or mechanistic studies of fiber in patients with IBS. In a crossover comparison of 30 g/day bran or placebo bran in 18 patients, bran increased stool weight and shortened intestinal transit time, but symptoms were not assessed.¹⁰⁸ Another crossover study in 14 patients used 15.6 g/day of fiber versus 2.7 g/day (placebo group) and identified significant effects with the first treatment, either bran or placebo,¹⁰⁹ a frequent finding in crossover studies of a disorder with high placebo responses. A study from India identified correlations between dose of ispaghula (10–30 g/day) and symptoms and stool weight, but not with whole-gut transit time.¹¹⁰ The authors also reported a significant effect of fiber on symptoms, but there was no placebo arm, and 4 of 14 patients were not included in the final analysis because of drop-out. An 80-patient crossover study of bran versus placebo identified no difference in overall responses and worse “wind-related” symptoms in the bran-treated group.¹¹¹ Francis and Whorwell¹¹² reported exacerbation of symptoms at the start of treatment that persisted long-term, particularly with citrus fruits.

In practice, many patients complain of bloating with higher doses of fiber. Bran is reported to be no better than placebo in relief of overall IBS symptoms¹¹¹ and may be worse than a normal diet¹¹² for some symptoms of IBS caused by intraluminal distention¹¹³ by bowel gas produced by bacterial fermentation of fiber.^{114,115} Fiber may induce bloating by increasing residue loading and bacterial fermentation without accelerating the onward movement of the increased residue.¹¹⁶

Notwithstanding these limitations, there is a significant improvement in constipation if sufficient quantities of fiber (20–30 g/day) are consumed.^{100,117} The uncertain benefits of fiber are the basis for the common practice of starting with a low dose, increasing gradually, and abandoning high levels of supplementation (e.g., >30 g/day)

if patients experience worsening of symptoms.¹¹² Thus, in summary, whereas fiber has a role in treating constipation, its value in the relief of abdominal pain and diarrhea associated with IBS is controversial. The efficacy of fiber in the long term is also questionable because it resulted in equivocal benefit in a group of 14 patients with IBS who were followed up for up to 3 years.¹¹⁸

Loperamide and Antidiarrheal Agents in IBS

Diarrhea-predominant IBS is associated with acceleration of small bowel and proximal colonic transit and responds to opioids.¹¹⁹ Most prefer to use loperamide over diphenoxylate, which contains atropine and may induce adverse effects that may be worrisome in the elderly, e.g., bladder dysfunction, glaucoma, and tachycardia. Loperamide (2–4 mg, up to 4 times daily), a synthetic opioid, decreases intestinal transit, enhances intestinal water and ion absorption, and increases anal sphincter tone at rest.¹¹⁹ These physiologic actions seem to explain the improvement in diarrhea, urgency, and fecal soiling observed in patients with IBS.¹¹⁹ The effect on resting anal tone¹²⁰ may help reduce fecal soiling at nighttime, when the internal anal sphincter function is the predominant mechanism of continence at a time when it is enhanced by the voluntary contraction of the external anal sphincter. Because it does not traverse the blood–brain barrier, loperamide is generally preferred to other opiates such as diphenoxylate, codeine, or other narcotics for treating patients with IBS who have predominant diarrhea and/or incontinence. Clinically, loperamide can also be used to reduce postprandial urgency associated with a prominent colonic response to feeding or as a means of improving control at times of anticipated stress or other colonic stimuli (e.g., exercise, social gatherings). One of the drawbacks of opioids is the tendency to induce constipation. As a result, the dose should be titrated for the individual patient, and the use of the liquid formula of loperamide is helpful. A recent study also showed reduced intensity of pain associated with improved stool consistency and reduced frequency of defecation. However, the patients treated with loperamide also experienced increased nightly abdominal pain.¹²¹ Symptoms of patients with constipation-predominant IBS given loperamide are not improved.¹²²

Cholestyramine is considered a third-line treatment in IBS with predominant diarrhea because of poor palatability and low patient compliance. The rationale for its use is based on the documentation of bile acid malabsorption in some patients with functional, typically painless diarrhea^{123,124} that mimics IBS with diarrhea. Cholerrheic diarrhea is most typically confirmed by a

therapeutic trial, although it can be diagnosed with $^{75}\text{SeHCAT}$ retention test or measurement in serum of 7α -hydroxycholesten-3-one¹²⁵ in a few centers. Bile acid sequestration may relieve the cholerrheic effect of bile acids in patients who have idiopathic bile acid malabsorption.¹²⁶ However, it is conceivable that a component of bile acid malabsorption may result from rapid ileal transit. The simpler, often more acceptable approach for patients who find cholestyramine distasteful would be to use loperamide as a first measure for bile acid malabsorption.

Use of Smooth Muscle Relaxants in IBS?

As noted previously by Klein,⁸⁶ the field of antispasmodic and anticholinergic therapy in IBS is bedeviled with methodologic problems. In many trials, significant numbers of patients drop out during follow-up (up to 60%), and high placebo response rates (as high as 69%) are noted. Nevertheless, full randomized, double-blind, placebo-controlled studies⁹ of at least 2 weeks' duration show that abdominal pain was relieved in 68% (mean range, 23%–87%) for active medication and 31% (mean range, 22%–66%) for placebo. Similarly, for global assessment, mean responses to drug and placebo were 73% (range, 39%–89%) and 41% (range, 13%–69%), respectively. Meta-analysis of available studies suggests that some of these agents, such as mebeverine, octylonium, and cimetropium,^{9,127} may be effective although the trial methodology was inadequate by modern standards.⁸⁶ In the meta-analysis by Poynard et al.¹²⁷ of smooth muscle relaxants in IBS, 5 drugs showed efficacy over placebo: cimetropium bromide (an antimuscarinic compound); pinaverium bromide and octylonium or otulinium bromide (quaternary ammonium derivatives with calcium-antagonist properties); trimebutine (a peripheral opiate antagonist); and mebeverine (a derivative of β -phenyl-ethylamine that has antimuscarinic cholinergic activity). None of these drugs underwent extensive trials in North America or received approval from the Food and Drug Administration. The commonly prescribed dicyclomine and hyoscine were not effective in the meta-analysis. Eight trials of peppermint oil for IBS, including a meta-analysis of 5 placebo-controlled, double-blind trials, have not established a role for this treatment in IBS.¹²⁷

In clinical practice, antispasmodics and anticholinergic agents are best used on an as-needed basis up to 2 times per day for acute attacks of pain, distention, or bloating. Agents such as dicyclomine or mebeverine seem to retain efficacy when used on an as-needed basis but become less effective with long-term use. Clidinium is no longer available as a separate drug and is combined with a benzodiazepine, chlorodiazepoxide. Although

these drugs have generally fallen out of favor, it remains to be conclusively demonstrated that the newer medications (discussed below) are actually superior for pain in IBS in head-to-head comparisons. This has been demonstrated in a phase III trial of alosetron versus mebeverine (discussed below). The development of more gastrointestinal-specific agents with antispasmodic or anticholinergic activity and fewer adverse effects (e.g., salivation, bladder, cardiac dysfunction) may lead to more effective use of this class of agents.

Psychotropic Agents

To date, psychotropic agents have probably been best reserved for those patients with diarrhea and pain-predominant IBS.⁸ However, there is increasing interest in the potential application of selective serotonin reuptake inhibitors (SSRIs), which tend not to cause constipation and may even induce diarrhea in some patients. One uncontrolled study¹²⁸ supports the efficacy of SSRIs in treating patients with IBS.

Tricyclic agents (e.g., amitriptyline, imipramine, doxepin) are now frequently used to treat patients with IBS, particularly those with more severe or refractory symptoms, impaired daily function, and associated depression or panic attacks. Initially they were used because a high proportion of patients with IBS reported significant depression.^{129–131} Antidepressants have neuromodulatory and analgesic properties, which may benefit patients independently of the psychotropic effects of the drugs.¹³⁰ It seems that the clinical effects of agents such as amitriptyline result from their central actions. Thus, amitriptyline had no significant effects on esophageal and rectal sensory thresholds and compliance in healthy subjects,¹³² and clinical benefit in the functional upper gastrointestinal disorder nonulcer dyspepsia seemed to be associated with better sleep rather than changes in gastric sensitivity.

Neuromodulatory effects may occur sooner and with lower doses in IBS patients than the doses used in the treatment of depression (e.g., 10–25 mg amitriptyline or 50 mg desipramine). Because antidepressants must be used on a continual rather than an as-needed basis, they are generally reserved for patients with frequently recurrent or continual symptoms. A 2–3-month trial is usually needed before a therapeutic benefit can be excluded.

The placebo-controlled trials of antidepressants in IBS have been summarized elsewhere.⁸ In 2 large studies,^{133,134} trimipramine decreased abdominal pain, nausea, and depression but did not alter stool frequency. The beneficial effect seems to be greater in those with abdominal pain and diarrhea. For example, desipramine improved abdominal pain and diarrhea,¹³⁵ whereas in an

earlier study¹²⁹ that combined patients with diarrhea and those with constipation, there was no significant benefit for desipramine over placebo. Nortriptyline, in combination with fluphenazine, reduced abdominal pain and diarrhea in 2 studies.^{131,136} Antidepressants do not result in improvement in constipation-predominant IBS. However, this may reflect aggravation of constipation by the confounding anticholinergic effects. The role of serotonin-reuptake inhibitors, which may cause diarrhea,¹³⁷ is currently the focus of prospective studies.

Hypnotherapy and Other Psychologic Treatments

An alternative therapeutic strategy for patients with significant pain is to use hypnotherapy or psychotherapy, but these approaches are generally less readily available to the practicing physician.¹³⁸⁻¹⁴⁰ Factors indicating a favorable response to psychotherapy include predominance of diarrhea and pain, association of IBS with overt psychiatric symptoms, and intermittent pain exacerbated by stress.¹⁴⁰ In contrast, patients with constant abdominal pain do poorly with psychotherapy¹⁴⁰ or hypnotherapy.¹⁴¹ The role of psychologic treatments is discussed in detail in a recent review.⁸ In a systematic review of the literature, Talley et al.¹⁴² concluded that the efficacy of psychologic treatment for IBS has not been established because of methodologic inadequacy. Although 8 studies reported psychologic treatments superior to control therapy, 5 failed to detect a significant effect.

Alternative Therapies in IBS

Several reports have documented the greater use of alternative medicine consultations and therapies in IBS than in “organic” diseases such as Crohn’s disease, ulcerative colitis, and organic upper gut disorders; these include reports from the United Kingdom, Denmark, and Canada.¹⁴³⁻¹⁴⁵ Use of alternative medical care was

positively correlated with scepticism toward conventional medicine and negatively related to perceived health status and satisfaction with a university clinic’s physicians.¹⁴⁶ Efficacy of alternative therapies has been difficult to ascertain in view of the lack of controlled trials¹⁴⁷; however, a first parallel-group, placebo-controlled 16-week trial of alternative medicine has recently been reported. In this study, individualized or conventional Chinese herbal medicines significantly improved bowel symptom scores and global symptoms and reduced IBS-related interference with life relative to placebo, which was administered in a capsule and was designed to taste, smell, and look similar to a Chinese herb formula.¹⁴⁸ Patients receiving individualized Chinese herbal medicine continued to report benefits beyond the actual treatment period.¹⁴⁸

5-HT₃ Antagonism in IBS

In the past several years, there have been significant improvements in the design of therapeutic trials. These improvements include better characterization of patient subgroups, exclusion of physiologic disturbances that overlap with or complicate IBS (such as pelvic floor dyssynergia), and use of appropriately powered studies with patient-derived, definable, clinically relevant global endpoints.

Serotonin type 3 and 4 receptors are involved in sensory (Figure 2) and motor (Figure 3) functions of the gut, and are targets for pharmacotherapy in IBS (Table 7).

Alosetron hydrochloride, a selective 5-HT₃ antagonist, is effective in relieving pain (Figure 4), normalizing bowel frequency, and reducing urgency in female patients with diarrhea-predominant IBS.¹⁴⁹ Alosetron was recently approved for the treatment of women with IBS whose predominant bowel symptom is diarrhea. 5-HT₃ receptors are extensively distributed on enteric motor

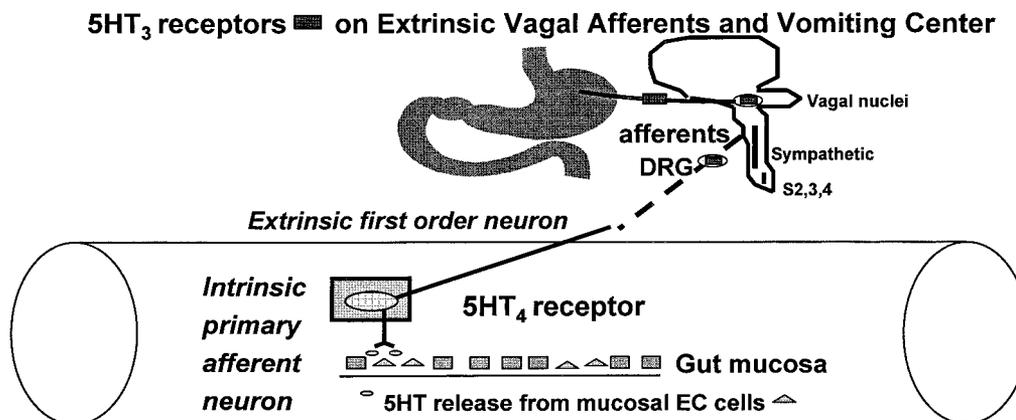


Figure 2. Location of 5-HT₃ and 5-HT₄ receptors on sensory apparatus related to the gastrointestinal tract. 5-HT₃ receptors are located on vagal afferents and in dorsal root ganglion (DRG) nerve cell bodies, as well as in the vomiting center. 5-HT₄ agonists have been shown to reduce visceral afferent firing during nociceptive stimulation. Reprinted with permission from the American College of Gastroenterology, 2000, Vol 95, pp 2698-2709.¹⁷⁶

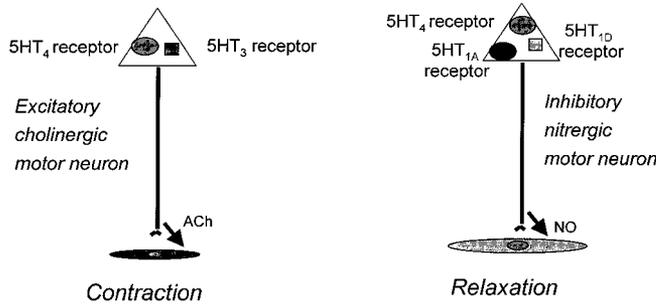


Figure 3. Location of serotonin type 3 (5-HT₃) and 4 (5-HT₄) receptors on intrinsic neurons in the myenteric plexus. A 5-HT₄ agonist induces muscle contraction by stimulation of excitatory cholinergic neurons; such an agonist also has potential to stimulate inhibitory nitrenergic neurons, causing viscus relaxation. The latter has been demonstrated in human stomach. Reprinted with permission from the American Journal of Gastroenterology, 2000, Vol 95, pp 2698–2709.¹⁷⁶

neurons and in peripheral afferents and central locations such as the vomiting center. Antagonism of these receptors reduces visceral pain, colonic transit, and small intestinal secretion. Clinical pharmacology studies of alosetron suggest that it dose-dependently reduces the arterial depressor response to noxious rectal distention in rats¹⁵⁰; relaxes the colon, increasing thresholds for volume-associated distentions in IBS patients¹⁵¹; and retards small bowel and colonic transit in IBS patients, with significantly greater effects in female than in male patients.¹⁵² Alosetron is rapidly absorbed after oral administration, with peak plasma concentrations after 1 hour. The drug can be taken with or without food.

In large placebo-controlled trials, alosetron was more effective than placebo in inducing adequate relief of pain and discomfort and improvement in bowel frequency, consistency, and urgency^{153–155} in women with diarrhea-predominant IBS. Another study compared alosetron (1 mg twice daily) with mebeverine, an antispasmodic approved in Europe for treatment of IBS, and showed similar results over the active comparator.¹⁵⁶

The beneficial response for pain and bowel dysfunction was observed within 1–4 weeks of the start of therapy

and was sustained throughout the duration of the trial. Within 1 week after discontinuation of the drug, symptoms were comparable to those in women receiving placebo. Benefit was observed only in female patients with diarrhea-predominant IBS symptoms, and further studies in male patients are awaited.

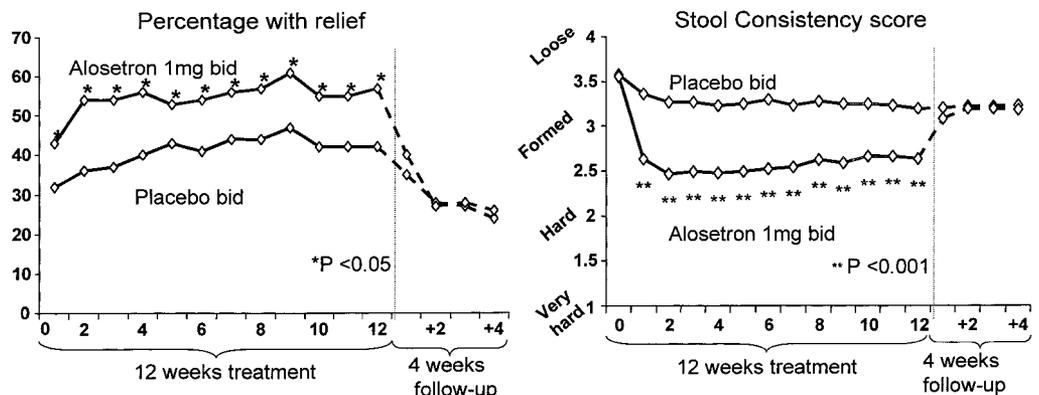
The most common adverse event with alosetron treatment is constipation, which in one trial was significantly more common among women receiving alosetron than among those receiving placebo (28% vs. 5%). The majority of patients reporting constipation had mild to moderate symptoms; only 10% of those patients withdrew from the study because of constipation. A significant adverse event with an unclear relationship to alosetron is acute ischemic colitis, estimated to occur in 0.1%–1% of patients. The reported cases resolved after several days to weeks without sequelae. Risk factors were not identified. The manufacturer initially recommended that the drug should be discontinued in patients who experience rectal bleeding or a sudden worsening of pain. This medication was withdrawn from the market in November 2000. Other drugs in this class (e.g., cilantezon) are being studied.

Experimental Medications for IBS

The availability of agents with visceral analgesic and sensorimotor-modulatory properties have stimulated much interest in the field of IBS therapy (Table 7). These include the κ-opioid agonist fedotozine,¹⁵⁷ other 5-HT₃ and 5-HT₄ antagonists, other serotonergic agents, and NK antagonists, some of which are now becoming available for routine clinical usage.

New partial or full 5-HT₄ agonists appear promising in the treatment of constipation or constipation-predominant IBS and are in phase III trials. The partial agonist tegaserod was recently shown to enhance peristalsis in an in vitro model and to do so at least in part by stimulating the intrinsic primary afferent neuron, activating excita-

Figure 4. Effect of alosetron and placebo on adequate relief of pain and stool consistency seen in female patients with diarrhea-predominant IBS. Note the rapid onset of symptom relief and persistence of effect until cessation of medication (vertical line at 12 weeks). Reprinted with permission.¹⁵⁵



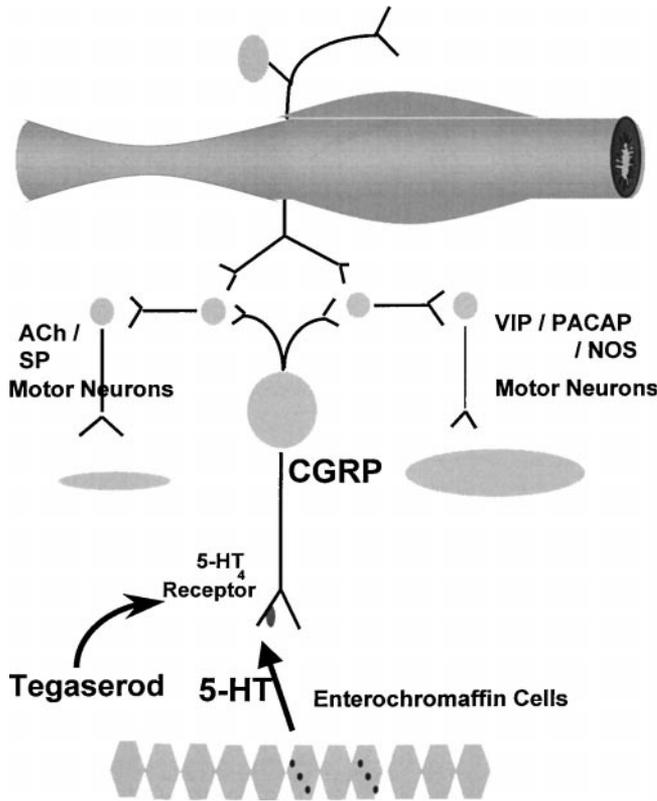


Figure 5. Model of the effect of serotonin on activation of intrinsic primary afferent neurons in the lamina propria after being released from enterochromaffin cells. Similarly, this figure depicts the effect of absorbed tegaserod, a partial 5-HT₄ agonist, on activation of intrinsic primary afferent neurons (e.g., releasing calcitonin gene-related peptide, CGRP), which in turn stimulate myenteric neurons to activate the “peristaltic reflex.” This involves an oral contraction, mediated through excitatory transmitters such as acetylcholine (ACh) or substance P (SP), and a caudad relaxation, mediated through inhibitory neurotransmitters such as vasoactive intestinal peptide (VIP), pituitary adenylate cyclase–associated peptide (PACAP), or nitric oxide synthase (NOS). Adapted and reprinted with permission.¹⁵⁸

tory and inhibitory intrinsic neurons that result in ascending contraction and descending relaxation, respectively (Figure 5¹⁵⁸). Tegaserod may also stimulate motility via a systemic action because it increases small

bowel and colonic contractions after intravenous administration in the dog.¹⁵⁹ It reduces visceral afferent firing during rectal distention and reduces abdominal contractions in response to noxious rectal distention, a pseudoaffective model of visceral pain.¹⁶⁰ Tegaserod reduces visceral afferents firing during noxious rectal distention.¹⁶¹

Tegaserod results in global relief of IBS symptoms in female patients with constipation-predominant IBS.¹⁶² The effective doses of tegaserod are 4–12 mg/day in 2 divided doses (2 mg or 6 mg twice daily). Tegaserod resulted in significant relief of the subjects’ global assessment of relief at the study endpoint, which was preset at the last 4 weeks of a 12-week trial. Global relief was measured as at least “somewhat relieved” for all 4 weeks or “complete/considerable relief” of IBS symptoms. It had been demonstrated that “somewhat” relief was associated with significant improvement of a number of secondary endpoints such as pain-free days, frequency of bowel movements, and stool consistency (Figure 6). To date, the tegaserod drug development program consisted of 3 phase III trials; one of the trials involved a titration step. Efficacy observed in the 3 trials was not uniform. However, pooled analysis shows significant benefit of tegaserod over placebo, and this was especially evident when subgroups were analyzed. Specifically, the drug is significantly effective with an approximately 15% advantage over placebo in female patients and in those with documented constipation during the baseline run-in period. Tegaserod’s greater efficacy over placebo was also more pronounced if patients who used laxatives more than 5 times during the 12-week study or took any laxative during the last 4 weeks of the study were included.¹⁶³

Tegaserod also appeared to provide benefit on several secondary endpoints assessed by daily diary responses, e.g., daily pain score, bloating score, and frequency and consistency of bowel movements. The effect on bloating, in particular, deserves further study, because this would

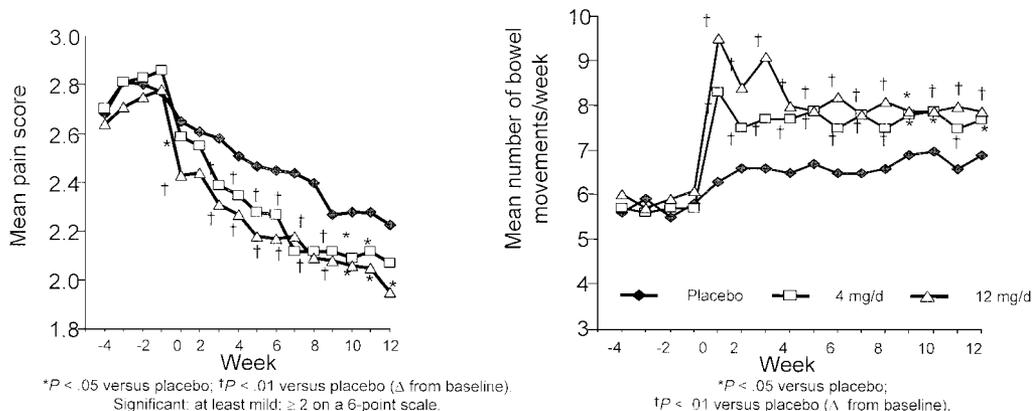


Figure 6. Effect of tegaserod on weekly assessment of mean pain score and number of bowel movements in patients with constipation-predominant IBS. Data on file at Novartis Pharmaceuticals; presented at the Advisory Committee Meeting of the Food and Drug Administration, June 2000.

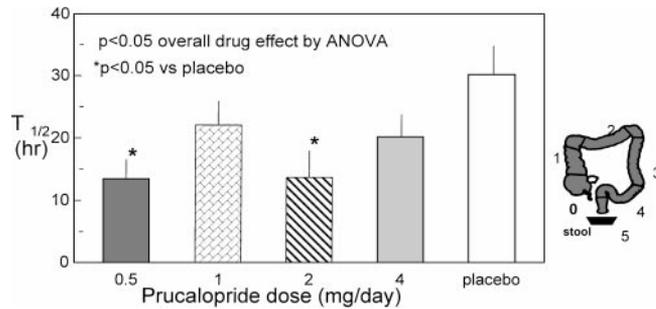


Figure 7. Effect of prucalopride on rate of emptying of the ascending and transverse colon in healthy participants. Note the overall acceleration of transit on prucalopride compared with placebo and the lack of a significant dose-related effect. Reprinted with permission.¹⁶⁶

be the first demonstration that any medication has a significant impact on this enigmatic symptom. The efficacy of tegaserod on bloating would be consistent with the hypothesis that gas transit is abnormal and a potential target for pharmacotherapy.^{73–75} Tegaserod appears quite safe. No serious adverse events have been reported in the clinical trials program and in the cohort treated in open evaluation for more than 6 months. It is anticipated that the medication will be approved for prescription in 2001.

The full 5-HT₄ agonist prucalopride induces strong contractions in the proximal colon *in vivo* in dogs¹⁶⁴ and accelerates colonic transit in healthy participants (Figure 7)^{165,166} and, most importantly, in patients with functional constipation.¹⁶⁷ Prucalopride induced a significant increase in the number of spontaneous and complete bowel movements in phase II trials of patients with functional constipation.^{168,169} Although this group is theoretically distinct from those with constipation-predominant IBS, the differences in these 2 subgroups of patients are probably small, and in clinical practice, patients often receive both diagnoses at different times. The effects of prucalopride on abdominal pain have not been thoroughly assessed, and further studies are needed. However, phase III clinical trials are currently on hold while a more thorough evaluation of potential intestinal carcinogenicity in animal species is evaluated.

Other investigational agents and new approaches (Table 7) that are currently being explored in phase II studies include newer type 3 antimuscarinic agents, cholecystokinin antagonists, the α_2 -adrenergic agonists, clonidine,¹⁷⁰ a 5-HT₁ agonist, buspirone,¹⁷¹ and an SSRI, citalopram.¹⁷² At doses of up to 0.3 mg, clonidine has been shown to reduce sensation of gastric and colonic distentions in health without significantly altering gastrointestinal or colonic transit. Clonidine also enhances rectal compliance in health and in IBS.^{173,174} Formal trials of its clinical efficacy are awaited.

Buspirone reduces gastric and colonic responses to volume distentions¹⁷¹ and may similarly have potential in functional disorders. Citalopram reduces colonic sensation to volume distention.¹⁷² Buspirone's anxiolytic activity may have an impact on the symptomatic benefits demonstrated in a small clinical trial.¹⁷¹ Similarly, the sensory and motor effects of citalopram must be evaluated in IBS patients.

Neurokinin antagonists also have therapeutic potential in IBS. Three types of receptor antagonists have been developed and confer benefit through their effects on smooth muscle, intrinsic excitatory neurons, and visceral afferents. Pharmacodynamic studies need to be performed to clarify the subgroups of IBS patients most likely to respond to these agents.

Bloating remains a significant symptom, for which no there is no evidence-based effective therapy. As noted above, tegaserod, a colonic prokinetic, has shown some efficacy on bloating in the phase III program. The parenterally administered anticholinesterase neostigmine reduces experimentally induced intestinal gas, with reduced abdominal girth. However, it also results in a significant increase in abdominal cramping.¹⁷⁵ The prokinetic approach is promising as a means to reduce abdominal bloating, but proper studies in IBS patients with predominant bloating are needed.

Summary and Conclusion

Management of IBS involves positive diagnosis, limited exclusion of organic disease, and reassurance. With insights into enteric neuroscience and a greater understanding of the brain–gut axis, novel therapies are being developed that make a more comprehensive approach possible. Much has been learned about this condition and the ways to study the pathophysiology and develop clinical trials in IBS. The role of infectious agents and neuroimmune interactions and the neurotransmitters involved in pain mediation will be clarified in the next decade and will enhance the management of IBS. However, development of optimal therapies will require collaboration between gastroenterologists, basic neuroscientists, pain pharmacologists, applied physiologists, and clinical trialists.

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