AMERICAN HEALTH CONSULTANTS®

Primary Care Reports™

The Practical, Peer-Reviewed Journal for Primary Care and Family Physicians

Volume 7, Number 5 **March 5, 2001**

Irritable Bowel Syndrome

Author: **Steven R. Peikin, MD**, Professor of Medicine; Head, Division of Gastroenterology and Liver Diseases, Department of Medicine, Cooper Hospital/University Medical Center, Camden, NJ.

Editor's Note—*The irritable bowel syndrome (IBS) is characterized by abdominal discomfort, altered bowel habits, and the absence of identifiable structural or biochemical abnormalities. IBS remains one of the most common diagnoses made by physicians and the most common cause for referral to gastroenterologists.*[1,2] *The prevalence of IBS varies with the population studied and the criteria used to define the disorder. In the United States and most of the Western Hemisphere, up to 10-20% of the adult population suffers from IBS,*[3] *the majority of whom do not seek medical care.*[4] *Recent studies suggest that the prevalence of IBS appears to be similar in all age groups*[5] *although the onset is most commonly between the ages of 20 and 30 years.*[6] *The prevalence is greater in women;*[7] *however, in India the female:male ratio is reversed, and this may reflect differences in health-seeking behavior rather than disease prevalence.*[8] *The prevalence of IBS appears to be similar between Caucasian and African Americans but may be lower in Hispanics.*[9] *The economic burden of IBS is substantial in the United States, with one study estimating the annual health care cost to be $8 billion.*[10] *IBS was also reported to be the second leading cause of absenteeism from work behind the common cold.*[11] *In a British study, 8% of IBS patients retired early due to their symptoms.*[12]

Pathogenesis of IBS

The pathogenesis of IBS is still unclear and cannot be explained by one single mechanism. At least 4 different factors seem to play a role: psychosocial, luminal, gut motility, and visceral hypersensitivity.

Psychosocial factors. Stress is well known to cause exacerbation of symptoms and determines how the illness is experienced and acted on by the patient. Patients with IBS who seek medical attention have a higher incidence of psychological problems than patients who do not.[13] Several studies have shown an increased prevalence of psychiatric disorders in patients with IBS (42-61%) including anxiety, mood disorders, and somatization.[14] A high incidence of physical and sexual abuse in childhood (30-56%) has been found in patients with functional gastrointestinal disorders.[15] Whitehead and coworkers believe that the development of functional bowel disorders is a learned illness behavior reflecting the ways in which parents respond to illness complaints in their children.[16]

Luminal factors. One-third of patients with IBS report that their symptoms began after an acute enteric infection.[17,18] When followed prospectively, 5-15% of patients presenting with acute gastroenteritis will go on to develop IBS-like symptoms.[19] Based on animal studies, some investigators have proposed that inflammatory infiltrates associated with mast cell proliferation caused by sensitization to toxins, food, or organisms leads to degranulation and liberation of histamine, which activates the enteric nervous system and contributes to the development of IBS (the so-called brain-mast cell connection).[20]

Gut motility. Several abnormalities of colonic and small intestinal motility have been described in patients with IBS and related functional bowel disorders. In some studies, provocative stimuli (meal ingestion, sham feeding, intra-

venous cholecystokinin, deoxycholic acid by mouth, rectal balloon inflation) demonstrate an increase in the intensity and duration of motor activity in IBS patients compared to healthy volunteers.[21] No consistently abnormal motor patterns have been described in patients with IBS in the fasting state. Extraintestinal motor abnormalities have been described in patients with IBS. Disorders of esophageal peristalsis, gastric dysrhythmias, impaired gallbladder contraction, sphincter of Oddi dysfunction, hyperactivity of the airway, postmethacholine, and detrusor instability have all been described in IBS patients.[21]

Visceral hypersensitivity. Ritchie and associates were the first to show that patients with IBS have a lower pain threshold in response to balloon distention of the sigmoid colon.[22] In contrast, IBS patients have a normal or even increased cutaneous pain threshold.[23] Several mechanisms have been proposed to explain the increased visceral sensitivity found in IBS patients:[9]

- Altered receptor sensitivity at the viscus itself.
- Increased excitability of the spinal cord dorsal horn neurons.
- Altered central modulation of sensation.

A recent study using positron emission tomography (PET) scanning to measure regional cerebral blood flow demonstrated that rectal distention in patients with IBS activates the prefrontal cortex (PFC), which amplifies pain perception.[24] Rectal distention in normal subjects activates the anterior cingulate cortex (ACC), an area of the limbic system associated with active opiate binding that reduces pain perception. These findings were contested by a more recent study using functional magnetic resonance imaging to detect central nervous system (CNS) activity during painful and nonpainful visceral stimulation.[25] The data suggested a normal pattern of activation of pain centers in IBS patients without aberrant CNS regulation and even a more pronounced activation of the ACC in patients with IBS compared to control subjects. Visceral hypersensitivity has also been reported to be caused by an increased visceral afferent response to normal as well as painful stimuli mediated primarily by 5-hydroxytryptamine (5-HT).[26]

Table 1. The Rome II Criteria for Irritable Bowel Syndrome

Diagnostic Criteria

Abdominal discomfort or pain with 2 of the following 3 features for at least 12 weeks, not necessarily consecutive, during the past 12 months:

1. Relief with defecation
2. Onset associated with a change in the frequency of stool
3. Onset associated with a change in the form of stool

Supportive symptoms

1. Fewer than 3 bowel movements per week
2. More than 3 bowel movements per day
3. Hard or lumpy stool
4. Loose or watery stools
5. Straining during bowel movements
6. Fecal urgency
7. Feelings of incomplete evacuation of a bowel movement
8. Passage of mucus during a bowel movement
9. Sensation of abdominal fullness or bloating

Diarrhea-predominant

1 or more of 2, 4, or 6 and none of 1, 3, or 5

Constipation-predominant

1 or more of 1, 3, or 5 and none of 2, 4, or 6

Adapted from: Thompson WG, Longstreth GF, et al. Functional bowel disorders and functional abdominal pain. Gut 1999; 45(suppl II):43.

Diagnosis

For many years, IBS has been considered a "diagnosis of exclusion," but in the late 1970s, a symptom-based criteria was developed enhancing and simplifying the diagnosis of IBS.[27] This led to a consensus definition known as the Rome criteria (*see Table 1*). The Rome criteria were developed[28] and revised[29] by an international group of investigators who described symptom patterns, clinical features, and diagnostic criteria of 24 functional gastrointestinal disorders. The diagnosis of IBS involves careful history-taking to elicit positive symptoms consistent with the Rome criteria and exclusion of organic disease in a cost-effective manner based on the predominant symptoms. During the initial visit, effort should be made to develop a relationship with the patient allowing the physician to gather data and educate the patient about IBS. This relationship establishes the beginning of successful management. Educational material should be provided to support and expand the information given in the office.[30] A review of the patient's medications, dietary history (specifically lactose intolerance), and major life stress factors should be elicited. Physicians should show interest, compassion and concerns about the patient's condition and provide reassurance. The physical examination is generally unremarkable

Primary Care Reports™, ISSN 1040-2497, is published biweekly by American Health Consultants, 3525 Piedmont Rd., NE, Bldg. 6, Suite 400, Atlanta, GA 30305.

VICE PRESIDENT/GROUP PUBLISHER: Donald R. Johnston.
EDITORIAL GROUP HEAD: Glen Harris.
MANAGING EDITOR: Robin Mason.
ASSISTANT MANAGING EDITOR: Neill Larmore.
MARKETING PRODUCT MANAGER: Schandale Kornegay.
GST Registration Number: R128870672.
POSTMASTER: Send address changes to ***Primary Care Reports™***, P.O. Box 740059, Atlanta, GA 30374.

Periodical rate postage paid at Atlanta, GA.
Back issues: $23. Missing issues will be fulfilled by Customer Service free of charge when contacted within one month of the missing issue's date.

AMERICAN HEALTH CONSULTANTS™
THOMSON HEALTHCARE

Subscriber Information

Customer Service: 1-800-688-2421.

E-Mail Address: customerservice@ahcpub.com
Editorial E-Mail Address: robin.mason@ahcpub.com
World-Wide Web: http://www.ahcpub.com

Subscription Prices

United States
$299 per year (Student/Resident rate: $150).

Multiple Copies
1-9 additional copies: $269 each; 10 or more copies: $239 each.

Canada
Add GST and $30 shipping

Elsewhere
Add $30 shipping

For 50 AMA/AAFP Category 1/Prescribed hours, add $100.

Accreditation

American Health Consultants (AHC) designates this continuing medical education (CME) activity for up to 50 hours in Category 1 credit toward the AMA Physician's Recognition Award. Each physician should claim only those hours of credit that he/she actually spent in the educational activity.

AHC is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide CME for physicians.

This CME activity was planned and produced in accordance with the ACCME Essentials.

This program has been approved by the American Academy of Family Physicians as having educational content acceptable for Prescribed credit hours. Term of approval covers issues published within one year from the beginning distribution date of Jan. 1, 2001. This volume has been approved for up to 50 Prescribed credit hours. Credit may be claimed for one year from the date of this issue.

Questions & Comments

Please call **Robin Mason,** Managing Editor, at (404) 262-5517 or e-mail: robin.mason@ahcpub.com between 8:30 a.m. and 4:30 p.m. ET, Monday-Friday.

Statement of Financial Disclosure

In order to reveal any potential bias in this publication, we disclose that Dr. Peikin (author) serves on the Speaker's Bureau of Glaxo Wellcome.

and serves primarily to exclude other disorders. It may reveal a tender sigmoid colon and discomfort on rectal examination, or even pressure/pain over the abdominal aorta but nothing is specific.[31] Limited laboratory studies to screen for organic disease are recommended and should include: complete blood count, electrolytes, sedimentation rate, thyroid stimulating hormone, and stool for blood, ova, and parasites. In a recent study, Tolliver and colleagues found that erythrocyte sedimentation rate, thyroid profile, and parasitic examination had no diagnostic yield in the routine evaluation of patients with IBS.[32] In patients older than 50 years, colonoscopy or flexible sigmoidoscopy with barium enema should be offered. Other diagnostic studies depend on the symptom subtype and the response to initial treatment.[33] For example, in patients with constipation not responding to an increase in fiber intake, a test for colonic transit may be indicated (eg, sitzmark study). In patients with diarrhea not responding to a lactose-free diet and antidiarrheal agents, performing a lactose-hydrogen breath test, stool studies for osmolarity, electrolytes and laxatives, small bowel follow through, therapeutic trial of cholestyramine to rule out idiopathic bile salt catharsis, small bowel aspirate/biopsy for giardia lamblia, bacterial overgrowth and sprue, and a colonoscopy to exclude inflammatory bowel disease and microscopic or collagenous colitis may be considered. In patients with pain/gas/bloating, plain abdominal radiography should be the first step to rule out obstruction, and if negative, a trial of antispasmodics can be offered. If there is no response to antispasmodics, small bowel radiography, hydrogen breath test, CT scan, and gastrointestinal manometry can be considered (*see Table 2*). Other factors may change the evaluation strategy. These include the duration of symptoms, the change in symptoms over time, the age and sex of patient, the referral status of the patient, prior diagnostic studies, a family history of colorectal malignancy, and the degree of psychosocial dysfunction.

Management

General principles. The management of patients with IBS starts with the establishment of a positive, trusting and non-

Table 2. Practical Management of IBS

I. Symptom assessment

Rome II criteria

II. Limited screen for organic disease

- CBC, e-, ESR, TSH
- Stool for O&P, occult blood
- Flexible sigmoidoscopy/Ba enema or colonoscopy if > 50 yr

III. Symptomatic subgroup:

	Constipation	Diarrhea	Pain/gas/bloating
Review diet history	Yes	Yes	Yes
Additional tests	No	Lactose-H_2 breath test	Abdominal x-ray
Therapeutic trial	Roughage	Loperamide	Antispasmodic
	Osmotic laxative	Diphenoxylate/Atropine	

IV. If intractable symptoms, consider:

Colonic transit test	Stool Osm, e-, laxatives	Small bowel x-ray
Anal manometry + balloon expulsion	Jejunal aspirate for O&P	Trial of antidepressants
	Transit test: SB and colon	Carbohydrate breath test
Measure rectoanal angle	Rectal sensation	GI manometry
Rectal sensation/emptying	75SeHCAT test/cholestyramine	Balloon distention test
Defecating proctography		

Abbreviations: e- = electrolytes; O&P = ova and parasites; Ba = barium; Osm = osmolarity; SB = small bowel; 75SeHCAT = Selenium-75 labeled homotaurocholic acid test

Adapted from: Camilleri M, Prather CM. The irritable bowel syndrome: Mechanisms and a practical approach to management. Ann Intern Med. 1992;116:1001.

judgmental relationship between patient and physician. This is supported by the fact that patients with IBS have a 30-88% placebo response rate regardless of treatment.[9] Patients should be educated about the benign nature of their disease and the excellent long-term prognosis.[34] Physicians should set realistic expectations and involve the patient in their treatment to optimize results.[35] Patients should also be reminded that their illness is chronic in nature with periods of exacerbations and remissions and that it cannot be cured but may be managed with dietary changes, medications, and psychological therapies. Such an approach has been associated with a reduction in health care visits.[36]

Dietary Modification. Dietary modification constitutes an essential element of the therapeutic strategy for IBS. Although food does not cause IBS, it may aggravate symptoms in some individuals generally due to the effect of certain foods on intestinal reactivity. One of the most common dietary factors contributing to symptoms of IBS is lactose.[37] Similar to the general adult population, 40% of patients with IBS have lactose intolerance, which can aggravate some IBS symptoms. About 2% of patients thought to have IBS were found only to have lactose intolerance. Therefore, it is of utmost importance to rule out lactose intolerance in all patients with IBS symptoms. Patients should also be advised to eat slowly, avoid caffeine, alcohol, and products made with nonabsorbable artificial sweeteners such as sorbitol. Physicians should assist the patient in identifying foods that may exacerbate their symptoms like dried beans, fatty foods, or gas-producing foods (*see Table 3*).[9] Fiber supplements are widely recommended for treatment of IBS. Patients should be instructed to increase their fiber intake gradually up to 20-30 g/d.[38] Different fiber preparations are available but some recent studies have shown that calcium polycarbophil is preferred over placebo by IBS patients.[39] Psyllium appears to have greater effect on improving stool pattern, abdominal pain, and distention than bran.[40] Most studies have failed to show a substantial benefit for fiber supplements in patients with IBS because of high placebo response rates in clinical trials of fiber (63-71%) and enrollment of small numbers of patients.[41] Moreover, symptom relief was unrelated to the actions of fiber (lubrication of stool, formation of stool bulk, and binding bile acids).[42] For instance, Hillman and associates followed 14 patients with IBS over a period of 2-3 years and found equivocal results on long-term fiber therapy.[43] Symptoms improved in 7, were unchanged in 5, and were worse in 2. There was no correlation between the clinical course and the amount of fiber consumed. Thus, it appears that in most studies fiber is no better than placebo, and 15-20% of patients with IBS may experience worsening symptoms of bloating and distention. However, constipated patients may benefit from intensive fiber therapy.[44]

Drug Therapy. As recommended by Camilleri and Prather, drug therapy in patients with IBS is targeted to the predominant symptoms.[45] Different classes of medications are available to treat moderate-to-severe symptoms. They include antidiarrheal agents, smooth muscle relaxants, or antispasmodics, psychotropic agents and 5-HT4 agonists (for constipation). The efficacy of many agents has been difficult to demonstrate due to high placebo response rates, a fluctuating natural course of IBS, difficulty in defining end points and lack of long-term follow-up in most clinical studies. Because of conflicting data, Jailwala and colleagues recently conducted a systematic review of the published literature on the treatment of IBS.[46] They found that antispasmodic agents were beneficial for patients with abdominal pain, loperamide seemed to be effective in patients with diarrhea, fiber was comparable to placebo, psychotropic agent trials were of poor quality and inconclusive, alosetron (now off the US market) was associated with a better global improvement in woman, and fedotozine showed improvement of pain and bloating in only one trial.

Antispasmodics. These agents are the most commonly studied and prescribed drugs for the treatment of patients with IBS. Their efficacy relies on cholinergic function blockade that reduces motor contractility, especially after a fatty meal. Antispasmodics are responsible for diverse side effects including dry mouth, blurred vision, and urinary retention. They are prescribed generally on an as needed basis, one-half to one hour prior to meal, with an additional dose given at bedtime to maintain a more constant blood level in patients with more frequent and persistent symptoms. Sublingual preparations are sometimes used for a more rapid onset of action. Antispasmodics often lose their efficacy with chronic treatment. Of the antispasmodics available in the United States (*see Table 4*), dicyclomine is the most widely used although efficacy was supported by only one trial.[47] In this trial, the dosage used for dicyclomine was 40 mg q.i.d., and most patients treated experienced anticholinergic side effects (69% compared with 16% of controls). A more recent meta-analysis by Poynard and col-

Table 3. Foods and Flatus Production

Normoflatulogenic Foods

- Meat, fowl, and fish
- Vegetables (eg, lettuce, cucumber, broccoli, pepper, avocado, cauliflower, tomato, asparagus, zucchini, okra, olives)
- Fruits (eg, cantaloupe, grapes, berries)
- Carbohydrates (eg, rice, corn chips, potato chips, popcorn, graham-crackers)
- Nuts
- Miscellaneous (eg, eggs, non-milk chocolate, flavored gelatin, fruit, ice)

Moderately Flatulogenic Foods

- Pastries
- Potatoes
- Eggplant
- Citrus fruit
- Apple bread

Extremely Flatulogenic Foods

- Milk and milk products
- Vegetables (eg, onions, beans, celery, carrots, brussel sprouts)
- Fruit (eg, raisins, bananas, apricots, prune juice)
- Miscellaneous (eg, pretzels, bagels, wheat germ)

Adapted from: VanNess MIA, Cattau EL. Flatulence: Pathophysiology and treatment. Am Fam Physician. 1985;31:198.

Table 4. Antispasmotic (anticholinergic) Agents

	Common brands (Route)	Formulations	Dosage Range/d
Phenobarbital/Scopolamine	Donnatal (PO)	Tablets, capsules	1-2 tabs/caps, t.i.d./q.i.d.
Hyoscyamine/Atropine		Elixer	5-10 cc, t.i.d./q.i.d.
		Extentabs	1 tab, q8-12h
Dicyclomine HCl	Bentyl (PO/IM)	Tablets, capsules (10, 20 mg)	10-20 mg, q.i.d.
		Syrup (10 mg/5 mL)	
		Injections (10 mg/cc)	10 mg, q.i.d.
Clidinium/Chlordiazepoxide	Librax (PO)	Capsules	1-2 caps, ac & hs
Hyoscyamine sulfate	Levsin (PO)	Tablets (0.125 mg)	1-2 tabs, q4h/pm
		Elixer, drops (0.125 mg/5 cc)	5-10 cc, q4h/pm
			Max 12 tabs/60 cc/d
	Levsin/SL (PO/SL)	Tablets (0.125 mg)	1-2 tabs, q4h/pm
	Levbid (PO)	Tablets ext rel (0.375 mg)	1-2 tabs, q12h
			Max 4 tabs/d

leagues reviewed 26 clinical trials comparing 5 different antispasmodics, none of which are approved for use in the United States, and found that these agents were significantly better than placebo for global assessment and abdominal pain.[48] Other agents, which have inhibitory effects on gastrointestinal motility without the anticholinergic effects, like calcium channel blockers (verapamil, nifedipine, nicardipine, octylonium bromide, pinaverium bromide, peppermint oil), smooth muscle relaxants (mebeverine, trimebutine), cholecystokinin antagonists (loxiglumide), and adrenergic agonists (clonidine, lidamidine) have not yet attained general acceptance or undergone extensive trials in the United States.[21]

Antidiarrheal agents. Loperamide is preferred over diphenoxylate/atropine or codeine because it does not cross the blood-brain barrier. The antidiarrheal effect is probably due to decreased intestinal transit, enhancement of intestinal water and ion absorption, and strengthening rectal sphincter tone.[49] Cholestyramine may be considered as a second-line treatment in patients with diarrhea predominant IBS or patients with idiopathic bile salt catharsis.

Psychotropic agents. Once believed to be beneficial due to the high incidence of depression in patients with IBS, it's now recognized that these agents have a dose-related neuromodulator and analgesic effect independent of their psychotropic effect.[50] Tricyclic antidepressants and selective serotonin reuptake inhibitors (SSRIs) are usually reserved for patients with severe or refractory symptoms. They may also be used in those individuals with associated depression or panic attacks. They are administered at low doses at bedtime (*see Table 5*). Most studies have evaluated treatment with tricyclic antidepressants rather than the SSRI. Only one uncontrolled review of antidepressant therapy supports the use of SSRIs in patients with IBS.[51] However, SSRIs seem to be preferred over tricyclic agents by most physicians and have been increasingly used due to their low side effect profile. In contrast to tricyclics, SSRIs seem to accelerate orocecal transit and may be considered for use in patients with constipation-predominant symptoms.[50] A new antidepressant agent, Mianserin, with 5-HT2 and 5-HT3 receptor antagonist and beta2-adrenoceptor antagonist effects, has been reported to decrease pain and functional disability compared to placebo.[52] Anxiolytics are generally not recommended because of potential for abuse, development of tolerance, and interaction with other drugs. Alone or in combination with anticholinergics, their use remains uncertain. Anxiolytics may be considered for brief periods to treat stress-related exacerbation of IBS.[35]

Hormonal Therapy. Since IBS occurs more frequently in women and its symptoms often coincide or worsen with the menstrual cycle, leuprolide acetate, a gonadotropin-releasing hormone analog, was tested in female patients with IBS in two double-blinded, randomized, placebo-controlled clinical trials.[53,54] The results of these trials showed a significant improvement in nausea, vomiting, bloating, abdominal pain, early satiety, and overall symptoms compared to placebo.

Serotonin receptor modulators. Some newer therapies for IBS focus on modulating neurotransmitter supply at different levels of the nervous system to create a disconnection between the brain and the gut. 5-HT is a major neurotransmitter in the gastrointestinal tract; 95% of 5-HT receptors are found within the enteric nervous system.[55] At least 14 subtypes have been identified of which 5-HT3 and 5-HT4 seem to play an important role in the pathophysiology of IBS.[56] In normal circumstances, 5-HT and norepinephrine (NE) antagonize each other to maintain an appropriate level of acetylcholine (Ach) release in the enteric nervous system. In constipation-predominant IBS, NE predominates, decreasing the bioavailability of Ach, which leads to a reduction in gastrointestinal contractility. In diarrhea-predominant IBS, 5-HT predominates and leads to an increase in Ach release and increased contractility. Actions of 5-HT include activation of secretory cells and afferent and efferent neurons, as well as a direct effect on gut smooth muscle leading to contraction or relaxation of the colonic wall.[56] The nature of the physiologic response to 5-HT is determined by the site of neurotransmitter release and by the type, number, and density of the 5-HT receptors in that location. The 5-HT3 antagonist (Alosetron) has been found to delay colonic transit, reduce colonic compliance and post-prandial gastrocolonic response, relax the left colon, attenuate the perception of volume

distention, increase fluid absorption in the small bowel, and improve stool consistency.[57] A randomized, placebo-controlled, double-blind clinical trial supports the use of Alosetron (Lotronex) in female patients with diarrhea-predominant IBS.[57] Significant benefit over placebo was seen with regards to abdominal pain, urgency, and stool consistency. Constipation was the most common side effect reported in 30% of subjects vs. 3% in the placebo group. The effect of Alosetron in male subjects is still under investigation but at the dose used in women (1 mg twice daily), the drug failed to show any benefit in men.[57] Alosetron was recently withdrawn from the US market due to reports of severe constipation that in a few cases had resulted in serious sequelae including ischemic colitis.

Activation of 5-HT4 receptors, located in gastrointestinal smooth muscle layers and nerve terminals of the myenteric plexus, causes inhibition of spinal afferent neurons, enhanced peristalsis, stimulation of chloride secretion and improvement in overall gastrointestinal symptoms.[58] Two drugs (Tegaserod and Prucalopride) are currently being evaluated in phase III clinical trials. Tegaserod, a partial 5-HT4 agonist, has been shown to increase colonic and orocecal transit by 20% compared to placebo.[59] In two pivotal double-blind trials,[60] patients

Table 5. Antidepressants and Their Effects on CNS Receptor Sites

Antidepressant	Anticholinergic Effect	5-HT Receptor Uptake	Histaminic Effects	Daily Dosage Range	Side Effects
TCAs					
Amitriptyline	++++	+++	++++	50-300 mg	Sedation, Orthostasis, Dry Mouth, Constipation
Desipramine	+	+++	+	50-300 mg	Diaphoresis, Dry Mouth, Orthostasis
Doxepin	++	+++	++++	50-300 mg	Sedation, Dry Mouth
Maprotiline	+	Nil	++++	100-150 mg	Orthostasis, Dry Mouth, Seizure, Sedation
Nortriptyline	++	+	++	75-150 mg	Dry Mouth
SSRIs					
Fluoxetine	Nil	+++	Nil	10 - 60 mg	N + V, Bruxism, H.A. Diarrhea
Fluvoxamine	Nil	+++	Nil	50 - 300 mg	N + V, Bruxism, H.A. Diarrhea
Paroxetine	Nil	++++	Nil	20 - 60 mg	N + V, Bruxism, H.A. Diarrhea
Sertraline	Nil	++++	Nil	50 - 200 mg	N + V, Bruxism, H.A. Diarrhea
Clornipramine	++++	+++	+	25 - 250 mg	Sedation
ATYP					
Bupropion	----	Nil	Nil	200-450 mg	Seizures (> 450 mg/d) Parkinsonian symptoms
Trazodone	Nil	+++	+++	50 - 600 mg 100 - 150 mg	Sedation, Priapism
Nefazodone	Nil	++	+++	200 - 600 mg 20 - 60 mg 50 - 200 mg	Sedation
Venlafaxine	Nil	+++	Nil	50 - 200 mg	N + V, Diarrhea

TCA = tricyclic antidepressant, SSRI = selective serotonin reuptake inhibitors, N+V = nausea and vomiting, H.A = headache, ATYP= atypical antidepressant

Adapted from: Drossman DA, Creed FH, Olden KW. Psychosocial aspects of the functional gastrointestinal disorders. In: Drossman DA, ed. Rome II The Functional Gastrointestinal Disorders. 2nd ed. McLean, Va: Degnon and Associates.

with constipation-predominant IBS were randomized to Tegaserod 4 mg/d, 12 mg/d or placebo. The 12 mg/d dose produced a significant increase in bowel movement frequency and relieved abdominal pain and discomfort compared to placebo; however, the results did not show any improvement in bloating. Most of the subjects were women so the results in men remain uncertain.

Prucalopride, a potent 5-HT4 agonist,[61] was evaluated in patients with chronic constipation in two large, phase III clinical trials.[62] Overall, 33% of patients receiving 2 mg of Prucalopride daily and 37% of those receiving 4 mg/d had a significant increase in the number of bowel movement. Only 10% of those in the placebo group improved.

Psychological Treatment. Psychotherapy has been reserved for patients with psychosocial features not responding to standard therapies. Several types of psychological treatments have been evaluated in IBS including: cognitive-behavioral therapy, biofeedback and stress reduction techniques, hypnosis, psychodynamics, or interpersonal psychotherapy.[63] There are no data available comparing these treatments to determine which one is superior, or to determine the efficacy for various subgroups of patients. Drossman and colleagues reviewed 15 studies that used a controlled design to compare psychological treatment with conventional medical treatment and concluded that the former appeared to be superior and that there were no differences in outcome based on the technique.[64] Furthermore, Heymann-Monnikes and associates evaluated 24 patients with IBS who were randomized to standardized multicomponent behavioral therapy (SMBT) in addition to standard medical therapy or standard medical treatment alone (SMT).[65] This study demonstrated the superiority of SBMT compared to SMT in improving IBS symptoms, overall quality of life, and sense of well being. Rectovisceral perception remained unchanged in both groups. In general, a positive response seems to be associated with patients younger than 50 years old who have stress-related exacerbation of symptoms, lower levels of anxiety, and intermittent rather than chronic pain.

Conclusion

IBS is the most common functional gastrointestinal disorder encountered in medical practice. The diagnosis is based on a set of criteria established by a consensus of experts and recently revised known as the Rome II criteria. No definite disease marker has been identified to help with a more objective diagnosis. IBS is thought to be caused by some abnormalities in brain-gut interaction. In the last 5 years, the importance of serotonin receptors in the pathogenesis of IBS and its role in modulating visceral sensitivity has been demonstrated. There appears to be some evidence that host and bacterial factors may play a role in IBS by altering visceral sensitivity. Therapy is usually focused on the predominant symptom. New therapies are emerging targeting 5-HT receptors with promising results.

References

1. American Gastrointestinal Association: Medical position statement: Irritable bowel syndrome. *Gastroenterology*. 1997;112:2118.
2. Thompson WG, Heaton KW, Smyth GT. Irritable bowel syndrome in general practice: Prevalence, characteristics and referral. *Gut*. 2000;46:78.
3. Talley NJ, Zinsmeister AR, Vandyke C. Epidemiology of colonic symptoms and the irritable bowel syndrome. *Gastroenterology*. 1991;101:927.
4. Talley NJ, Zinsmeister AR, Melton LJ. Irritable bowel syndrome in a community: Symptom subgroups, risk factors and health care utilization. *Am J Epidemiol*. 1995;142:76.
5. Talley NJ, O'Keefe EA, Zinsmeister AR Prevalence of gastrointestinal symptoms in the elderly: a population based study. *Gastroenterology*. 1992;102:1962.
6. Harvey RF, Mavard EC, Brown AM. Prognosis in the irritable bowel syndrome: A five-year prospective study. *Lancet*. 1987;1:963.
7. Harris SM. Irritable bowel syndrome. A cost effective approach for primary care physicians. *Postgraduate Medicine*. 1997;101:215.
8. Jain AP, Gupta OP, Jajoo VN. Clinical profile of irritable bowel syndrome at a rural based teaching hospital in central India. *J Ass Physicians India*. 1991;39:385.
9. Drossman DA, Whitehead WE, Camilleri M. Irritable bowel syndrome: A technical review for practice guideline development. *Gastroenterology*. 1997;112:2120.
10. Talley NJ, Gabriel SE, Harmsen WS. Medical costs in community subjects with irritable bowel syndrome. *Gastroenterology*. 1995;109:1736.
11. Walker EA, Gelfand AN, Gelfand MD. Psychiatric diagnoses, sexual and physical victimization, and disability in patients with irritable bowel syndrome or inflammatory bowel disease. *Psychol Med*. 1995;25:1259.
12. Rees GA, Davies GJ, Parker M. Gastrointestinal symptoms and diet of members of an irritable bowel self-help group. *J R Soc Health*. 1994;114:182.
13. Lynn RB, Friedman LS. Irritable bowel syndrome. *N Engl J Med*. 1993;329:1940.
14. Drossman DA, Creed FH, Olden KW. Psychosocial aspects of the functional gastrointestinal disorders. *Gut*. 1999;45(Suppl II):25.
15. Drossman DA, Talley NJ, Olden KW Sexual and physical abuse and gastrointestinal illness. Review and recommendations. *Ann Intern Med*. 1995;123:782.
16. Whitehead WE, Crowell MD, Heller BR Modeling and reinforcement of the sick role during childhood predicts adult illness behavior. *Psychosom Med*. 1994;6:541.
17. Neal KR, Hebden J, Spiller R. Prevalence of gastrointestinal symptoms six months after bacterial gastroenteritis and risk factors for development of the irritable bowel syndrome: Postal survey of patients. *BMJ*. 1997;314:779.
18. Gwee KA, Graham JC, McKendrick MV Psychometric scores and persistence of irritable bowel after infectious diarrhea. *Lancet*. 1996;347:150.
19. Gwee KA, Leong YL, Graham C. The role of psychological and biological factors in postinfective gut dysfunction. *Gut*. 1999;44:400.
20. Wood JD, Alpers DH, Andrews PLR. Fundamentals of neurogastroenterology. *Gut*. 1999;45(Suppl II):6.
21. Hasler WL, Chung O. Irritable bowel syndrome. In:Yamada, ed. *Textbook of Gastroenterology*. 3rd ed. Philadelphia, Pa: Lippincott, Williams and Wilkins; 1999.
22. Ritchie J. Pain from distention of the pelvic colon by inflating a balloon in the irritable bowel syndrome. *Gut*. 1973;6:105.
23. Cook IJ, van Eeden A, Collins SM. Patients with irritable bowel syndrome have greater pain tolerance than normal subjects. *Gastroenterology*. 1987;93:727.
24. Silverman DHS, Munakata JA, Ennes H. Regional cerebral activity in normal and pathologic perception of visceral pain. *Gastroenterology*. 1997;112:64.
25. Howard Mertz, Morgan V, Tanner G. Regional cerebral activation in irritable bowel syndrome and control subjects with painful and nonpainful rectal distention. *Gastroenterology*. 2000;118:84
26. Mayer EA, Gebhart GF Basic and clinical aspects of visceral hyperalgesia. *Gastroenterology*. 1994;107:271.
27. Manning AP, Thompson WG, Heaton KW. Towards positive diagnosis of irritable bowel. *BMJ*. 1978;2:653.
28. Thompson WG, Creed FH, Drossman DA. Functional bowel disorders and functional abdominal pain. *Gastroenterology International*. 1992;5:75.
29. Thompson WG, Longstreth GF, Drossman DA. Functional bowel disorders and functional abdominal pain. *Gut*. 1999;45(Suppl II):43.
30. Colwell LJ, Pratner CM, Phillips SF. Effects of an irritable bowel syndrome educational class on health promoting behaviors and symptoms. *Am J Gastroenterol*. 1998;93:901.
31. Baert D, Steger P, Kerschot E. Aortic pressure pain: Clinical significance. Any relationship to the irritable bowel syndrome? *J Clin Gastroenterol*. 1996;22:111.

32. Tolliver BA, Herrera JL, DiPalma JA. Evaluation of patients who meet clinical criteria for irritable bowel syndrome. *Am J Gastroenterol*. 1994;89:176.
33. Camilleri M, Choi MG. Review: Irritable bowel syndrome. *Aliment Pharmacol Ther*. 1997;11:3.
34. Harvey RF, Mauad EC, Brown AM. Prognosis in the irritable bowel syndrome: A five-year prospective study. *Lancet*. 1982;1:963.
35. Drossman DA, Thompson WG. The irritable bowel syndrome: review and a graduated multicomponent treatment approach. *Ann Intern Med*. 1992;116:1009.
36. Owens DM, Nelson DK, Talley NJ. The irritable bowel syndrome: Long-term prognosis and the physician-patient interaction. *Ann Intern Med*. 1995;122:107.
37. Mascolo R, Saltzman JR. Lactose intolerance and irritable bowel syndrome. *Nutr Rev*. 1998;56:306.
38. Friedman G. Diet and the irritable bowel syndrome. *Gastroenterol Clin North Am*. 1991;20:313.
39. Toskes PP Connery KL, Ritchey TW. Calcium polycarbophil compared with placebo in irritable bowel syndrome. *Aliment Pharmacol Ther*. 1993;7:87.
40. Snook J, Shepherd HA. Bran supplementation in the treatment of irritable bowel syndrome. *Aliment Pharmacol Ther*. 1994;8:511.
41. Klein KB. Controlled clinical trials in the irritable bowel syndrome: A critique. *Gastroenterology*. 1988;95:232.
42. Cook IJ, Irvine EJ, Campbell D. Effect of dietary fiber on symptoms and rectosigmoid motility in patients with irritable bowel syndrome. *Gastroenterology*. 1990;98:66.
43. Hillman LC, Stace NH, Pomare EW. Irritable bowel patients and their long term response to a high fiber diet. *Am J Gastroenterol*. 1984;79:1.
44. Camilleri M. Review Article: Clinical evidence to support current therapies of irritable bowel syndrome. *Aliment Pharmacol Ther*. 1999;13(Suppl II):48.
45. Camilleri M, Prather CM. The irritable bowel syndrome: Mechanisms and a practical approach to management. *Ann Intern Med*. 1992;116:1001.
46. Jailwala J, Imperiale TF, Kroenke K. Pharmacologic treatment of the irritable bowel syndrome: A systematic review of randomized, control trials. *Ann Intern Med*. 2000;133:136.
47. Page JG, Diraberger GM. Treatment of the irritable bowel syndrome with Bentyl (dicyclomine hydrochloride). *J Clin Gastroenterol*. 1981;3:153.
48. Poynard T, Naveau S, Mory B. Metaanalysis of smooth muscle relaxants in the treatment of irritable bowel syndrome. *Aliment Pharmacol Ther*. 1994;8:499.
49. Sun WM, Read NW, Verlinden M. Effects of loperamide oxide on gastrointestinal transit time and anorectal function in patients with chronic diarrhea and faecal incontinence. *Scand J Gastroenterol*. 1997;32:34.
50. Gorard DA, Libby GW, Farthing MJ. Influence of antidepressants on whole gut and orocecal transit times in health and irritable bowel syndrome. *Aliment Pharmacol Ther*. 1994;8:159.
51. Clouse RE, Lustman PJ, Geisman RA. Antidepressant therapy in 138 patients with irritable bowel syndrome: A five-year clinical experience. *Aliment Pharmacol Ther*. 1994;8:409.
52. Tanum L, Malt VF. A new pharmacologic treatment of functional gastrointestinal disorder. A double blind placebo ontrolled study with mianserin. *Scand J Gastroenterol*. 1996;31:318.
53. Mathias JR, Clench MH, Roberts PH. Effect of Leuprolide acetate in patients with functional bowel disease. Long term after double blind, placebo controlled study. *Dig Dis Sci*. 1994;39:1163.
54. Mathias JR, Clench MH, Abell TL. Effect of Leuprolide acetate in treatment of abdominal pain and nausea in premenopausal women with functional bowel disease: A double blind, placebo controlled, randomized study. *Dig Dis Sci*. 1998;43:1347.
55. Gershon MD. Roles played by 5-hydroxytryptamine in the physiology of the bowel. *Aliment Pharmacol Ther*. 1999;13(Suppl.2):15.
56. Humphrey PPA, Bountra C, Clayton N. Review article: The therapeutic potential of 5-HT3 receptor antagonists in the treatment of irritable bowel syndrome. *Aliment Pharmacol Ther*. 1999;13(Suppl.2):31.
57. Camilleri M, Northcutt AR, Kong S. Efficacy and safety of Alosetron in women with irritable bowel syndrome: A randomized, placebo-controlled trial. *Lancet*. 2000;355:1035.
58. Scott L, Perry CM. Tegaserod. *Drugs*. 1999;58:491.
59. Prather CM, Camilleri M. Tegaserod accelerates orocecal transit in patients with constipation-predominant irritable bowel syndrome. *Gastroenterology*. 2000;118:463.
60. Meuller-Lissner S, Fumagalli I, Bardhan K. Tegaserod, a 5-HT4 receptor partial agonist, relieves key symptoms of irritable bowel syndrome. Program and abstracts of Digestive Disease Week 2000; May 21-24, 2000; San Diego, Calif. Abstract 1000.
61. Bouras EP, Camilleri M, Burton DD. Selective stimulation of colonic transit by the benzofuran 5-HT4 agonist, Prucalopride, in healthy humans. *Gut*. 1999;44:682.
62. Johanson J, Miner P, Parkman H. Prucalopride improves bowel movement frequency and symptoms in patients with chronic constipation: results of two double blind, placebo-controlled trials Program and abstracts of Digestive Disease Week 2000; May 21-24, 2000; San Diego, Calif. Abstract 999.
63. Guthrie E, Creed F, Dawson D. A randomized, controlled trial of psychotherapy in patients with refractory irritable bowel syndrome. *Br J Psychiatry*. 1993;163:315.
64. Drossman DA, Creed FH, Olden KW. Psychosocial aspects of the functional gastrointestinal disorders. In: Drossman DA, Corazziari E, Talley NJ, Thompson WG, Whitehead WE, eds. *Rome II The Functional Gastrointestinal Disorders*. 2nd ed. McLean, Va: Degnon and Associates.
65. Heymann-Monnikes I, Arnold R, Florin I. The combination of medical treatment plus multicomponent behavioral therapy is superior to medical treatment alone in the therapy of irritable bowel syndrome. *Am J Gastroenterol*. 2000;95:981.

Physician CME Questions

22. Which of the following is characteristic of irritable bowel syndrome?
    a. Abdominal pain, reflux, weight loss
    b. Abdominal pain, altered bowel habits, absence of structural or biochemical abnormalities.
    c. Abdominal pain, nausea, bloody diarrhea
    d. Abdominal pain, headache, altered bowel habits.

23. Which of the following statements is true in patients with IBS?
    a. IBS patients have increased cutaneous sensitivity.
    b. Increased pain with air insufflation during barium enema or colonoscopy.
    c. 90% of patients with IBS seek medical attention.
    d. None of the above

In Future Issues:

Prostate Cancer—
Richard D. Williams, MD