REVIEW

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The challenge of irritable bowel syndrome: Creating an alliance between patient and physician

ABSTRACT

The most important component of the treatment of irritable bowel syndrome (IBS) is to establish a therapeutic physician-patient relationship, coupled with patient education. We describe a stepwise approach to management, including judicious use of invasive tests, and setting realistic treatment goals that address the dominant symptoms, their severity, and psychosocial factors.

KEY POINTS

It is desirable to make a positive diagnosis, rather than just determine IBS as a diagnosis of exclusion.

The pathophysiology is still not clear, but IBS is thought to result from an interaction between increased visceral hypersensitivity (hyperalgesia), abnormal gut motility, and psychosocial factors.

The characteristic symptom of IBS is abdominal pain or discomfort which is relieved with defecation, and is associated with change of stool frequency and form, in the absence of identifiable structural or biochemical abnormalities.

PATIENT INFORMATION
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IN PATIENTS SUSPECTED of having irritable bowel syndrome (IBS), the key for physicians is to develop a "therapeutic alliance" with the patient. Since IBS is a chronic disorder with no specific cause or cure, confidence in the diagnosis and educating and reassuring the patient are vital therapeutic tools.

We outline a stepwise approach to diagnosis and treatment, which seeks psychosocial factors as well as physiologic "red flags" for more serious conditions.

The stepwise management of IBS begins by:

- Making sure that the symptoms are consistent with IBS
- Selecting tests judiciously to make a positive diagnosis
- Deciding what treatment goals are realistic.

Overemphasis on identifying a specific organic cause for the symptoms may subject the patient to unnecessary and costly tests.

PREVALENCE AND IMPACT

IBS is one of the most common functional gastrointestinal disorders seen in clinical practice[1] and is the most commonly diagnosed gastrointestinal condition. Although estimates of the true prevalence vary widely from study to study due to the use of different diagnostic and population selection criteria and data sources, a reasonable estimate is that 10% to 20% of US adults report symptoms compatible with IBS. Only 15% of those affected actually seek medical attention.[2,3] IBS accounts for 12% of primary care and 28% of gastroenterological practice visits, and for 41% of all functional gastrointestinal disorders.[4]

The prevalence of IBS is similar in young adults and the elderly. Women are diagnosed more than twice as often as men.

The financial burden of IBS is high. In the United States, IBS results in an estimated $8 billion in direct medical costs annually.[5]

IBS has a major impact on quality of life. Social and professional life are affected, with increased absenteeism from work, missed job opportunities, and limited social interaction.[6]

A BIOPSYCHOSOCIAL DISORDER

So far, no physiologic mechanism unique to IBS has been identified. Currently, IBS is viewed as a biopsychosocial disorder resulting from an interaction between increased visceral hypersensitivity (hyperalgesia), abnormal gastrointestinal motility, and psychosocial factors.[7] Persistent neuroimmune interactions after infectious gastroenteritis may lead to sensory dysfunction, resulting in IBS symptoms.

Visceral hyperalgesia

Studies of balloon distention in the large and small bowel[8,9] have shown that patients with IBS are aware of the balloon sooner and experience pain at significantly lower balloon volumes than healthy subjects. It is not known at which level of pain-signal transmission (starting at the receptor in the gut wall, through the spinal cord to the brain) this increased sensitivity is expressed, but it is selective for visceral stimuli. Patients with IBS have normal or decreased sensitivity to somatic stimuli.[9,10]

Abnormal gastrointestinal motility

The changes in gut motility observed in IBS are quantitative, with no distinct pattern to distinguish affected patients from healthy subjects. Two major changes are observed:

- Enhanced gut transit in some patients with diarrhea as the predominant symptom, and the opposite in some patients with predominant constipation
- Increased motility compared with healthy subjects in response to stimuli such as psychological stress, meals, and balloon inflation in the gut.

Psychosocial factors

IBS has long been dismissed as a psychosomatic condition, as it has no clear cause or pathophysiologic features. Psychological stress and emotional events such as physical or sexual abuse can result in gastrointestinal symptoms in healthy subjects, but they affect patients with IBS to a greater degree.

Common psychological symptoms associated with IBS are depression, somatization, anxiety, hostility, phobia, and paranoia. Up to 50% of patients with IBS meet criteria for a psychiatric diagnosis, compared with 20% of those with organic gastrointestinal disorders and 15% of control subjects.[4] Although no psychological or psychiatric disorder is specific to IBS, identification of such disorders helps in planning psychological or psychopharmacologic treatment.

SYMPTOMS

Patients with IBS can present with a variety of gastrointestinal and extraintestinal symptoms. But the main symptoms are the complex of chronic abdominal pain and altered bowel habits in the absence of identifiable structural or biochemical abnormalities.

Chronic abdominal pain in IBS is usually described as a crampy sensation with variable intensity and periodic exacerbations. The pain is generally located in the lower abdomen, although the location and character of the pain can vary widely. Emotional stress and eating may exacerbate the pain, while defecation often provides some relief. Progressive pain that awakens the patient from sleep or prevents sleep should prompt a search for other causes.

Abnormal gastrointestinal motility can cause both diarrhea and constipation

Stool volume, frequency, consistency

Since the range of normal bowel habits is broad, a careful history of the volume, frequency, and consistency of the patient's stool is important. The frequency of bowel movements in healthy people can range from three times a day to three times a week. Patients with IBS complain of diarrhea, constipation, alternating diarrhea and constipation, or normal bowel movements alternating with diarrhea, constipation, or both.

Diarrhea

Diarrhea is generally characterized as frequent loose stools of small and moderate volume.

TABLE 1

A stepwise approach to the management of irritable bowel syndrome

STEP	ACTIONS	KEY POINTS
1	**Assessment of symptoms**	Use nonjudgmental, open-ended questions Identify predominant symptom Screen for psychological factors Identify "red flags" of other diseases: weight loss, fever, persistent diarrhea, rectal bleeding, nocturnal pain and abnormal bowel habit, new symptoms in patients ≥ 50 years of age, family history of gastrointestinal malignancy, inflammatory bowel disease, or celiac disease
2	**Physical examination**	Identify "red-flag" signs: anemia, jaundice, organomegaly, abdominal mass
3	**Laboratory tests**	Complete blood count, chemistry panel, thyroid-stimulating hormone, and stool studies indicated for most patients for both exclusion and inclusion of diagnosis
4	**Invasive tests**	Flexible sigmoidoscopy or colonoscopy indicated in selected patients, in particular: Age > 50 years, chronic stable symptoms Age > 50 years, recent onset Persistent diarrhea, rectal bleeding
5	**Treatment**	Tailored to patient's symptoms
6	**Follow-up**	Assess clinical response in 3 to 6 weeks

Bowel movements generally occur during waking hours, most often in the morning or after meals. Most bowel movements in patients with IBS are preceded by urgency and may be followed by a feeling of incomplete evacuation. Nocturnal diarrhea, bloody stools, dehydration, or weight loss are not features of IBS.

Constipation

Constipation in patients with IBS may last from days to months, with interludes of diarrhea or normal bowel function. Stools are often hard and may be described as pellet-shaped. Patients may also experience a sense of incomplete evacuation, even when the rectum is empty. This can lead to straining with defecation, prolonged time on the toilet, and inappropriate use of enemas or laxatives.

Other gastrointestinal symptoms

Upper gastrointestinal symptoms seen in patients with IBS include heartburn, dysphagia, nonulcer dyspepsia, nausea, and noncardiac chest pain.[11] Patients with IBS often complain of abdominal bloating and increased gas production in the form of flatulence or belching. However, these symptoms occur despite normal gastrointestinal gas volumes and absence of significant colonic distention.

In taking the history, ask nonjudgmental, open-ended questions

Extraintestinal symptoms

Patients with IBS often have nongastrointestinal complaints, including rheumatologic symptoms, headache, genitourinary symptoms such as urinary frequency and urgency, dyspareunia, sexual dysfunction, and sleep disturbances.[12–14]

DIAGNOSTIC CRITERIA

In the absence of a biologic marker, attempts have been made to standardize the diagnosis of IBS using symptom-based criteria. The most commonly used are those proposed by Manning in 1978[15] and the Rome II criteria, updated in 1999.[16]

The Manning criteria include relief of pain with bowel movements, looser and more frequent stools with onset of pain, passage of mucus, and a sense of incomplete evacuation.

The Rome II criteria include abdominal discomfort or pain for at least 12 weeks in the preceding 12 months (which need not be consecutive), with at least two of three features: relief with defecation, onset associated with a change in frequency of stool, and onset associated with a change in the appearance of stool. Supportive features include abnormal stool frequency and consistency, abnormal passage of stool, and bloating or abdominal distention. A key feature of the definition is the presence of abdominal discomfort or pain.

STEPWISE APPROACH TO DIAGNOSIS AND MANAGEMENT

Although it is important to exclude organic causes of symptoms compatible with IBS, overemphasis can subject the patient to unnecessary and costly testing. The emphasis should be on identifying a symptom complex compatible with IBS and then judiciously selecting diagnostic tests (TABLE 1). The Rome and Manning criteria provide guidelines for identifying patients with suspected IBS.

Explain that IBS symptoms are real but not life-threatening

Step 1: Careful assessment of symptoms

Use nonjudgmental, open-ended questions, including questions about dietary history and medications. Identify abdominal pain as the dominant symptom, with altered bowel function. Consider psychological factors, gently questioning about physical and sexual abuse, once a physician-patient relationship has been established.

Identify "red flag" symptoms such as weight loss, fever, persistent diarrhea, rectal bleeding, nocturnal symptoms of pain and abnormal bowel habit, new onset of symptoms in patients aged 50 and older, family history of gastrointestinal malignancy, inflammatory bowel disease, and celiac disease.

Step 2: Physical examination

The physical examination is generally normal in IBS. Patients may have nonspecific abdominal tenderness. Identify "red flag" signs such as anemia, jaundice, organomegaly, and abdominal mass.

Step 3: Laboratory tests

A complete blood count, chemistry panel, and thyroid function tests help to exclude organic diseases. Stool analysis for ova, parasites, and fecal leukocytes should be done if diarrhea is the predominant symptom.

Step 4: Invasive tests

Routine flexible sigmoidoscopy with biopsy has a low diagnostic yield and is not cost-effective, particularly in young patients. However, it may help to reassure an anxious patient, and it may be performed in elderly patients with chronic, stable symptoms.

Colonoscopy or, less preferably, flexible sigmoidoscopy combined with barium enema, is usually indicated to exclude a neoplasm in patients over age 50,[4,7] and if inflammatory bowel disease is suspected in younger patients. Mucosal biopsy should be performed to exclude microscopic colitis in patients with persistent diarrhea.

Step 5: Initiate treatment

See the discussion that follows.

Step 6: Follow-up in 3 to 6 weeks

GENERAL MANAGEMENT PRINCIPLES

Since IBS is a chronic disorder with no specific cause or cure, confidence in the diagnosis and educating and reassuring the patient are vital therapeutic tools. The overall treatment goal should be to relieve symptoms and address the patient's specific concerns.[7]

How to determine the patient's concerns

A simple way to determine the patient's concerns is to ask why he or she is seeking help at this time. Possible reasons may include:

- Recent exacerbating factors, eg, concurrent medical disorders, new medications, dietary changes
- Concern about serious illness, recent family death
- Environmental stressors, eg, major loss, abuse history

- Psychiatric comorbidity, eg, depression, anxiety
- Impairment of daily function, recent inability to work
- Hidden agendas, eg, disability claims, narcotic requests, laxative abuse, secondary gain.

An effective treatment strategy should address the dominant symptoms, their severity, and psychosocial factors.

How to establish a therapeutic physician-patient relationship

The most important component of treatment is to establish a therapeutic physician-patient relationship coupled with patient education (see the patient information page, "Controlling irritable bowel syndrome," page 237) as proposed by Drossman,[17] with the following steps:

- Obtain the history through a nonjudgmental and patient-centered interview
- Conduct a careful examination and order cost-efficient tests
- Determine the patient's understanding of the illness and his or her concern ("What do you think is causing your symptoms?")
- Provide information on proposed mechanisms of IBS; this helps to validate the patient's disease experience and sets the basis for therapeutic interventions
- Explain to patients that their symptoms are real and are not life-threatening, but that the disease is likely to be chronic and the diagnosis, if well established, is not likely to change, and that he or she can expect a normal life span
- Establish realistic expectations that have consistent limits and which acknowledge that IBS is a condition that can be managed, but not cured ("I appreciate how bad the pain is, but narcotic medication is not indicated"); involve the patient in treatment decisions ("Let me suggest some treatments for you to consider").

Dietary modification

A dietary history may reveal symptom patterns related to dairy or gas-producing foods. Excluding foods that increase flatulence (beans, onions, celery, carrots, raisins, apricots, prunes, brussels sprouts, wheat germ, pretzels, and bagels) should be considered in patients with symptoms of bloating or gas. Underlying visceral hyperalgesia in IBS may explain the exaggerated discomfort experienced with consumption of gas-producing foods.

Increased intake of fiber is generally recommended, through either diet or the use of commercial bulking supplements. Although the efficacy of fiber supplements has not been proven, some improvement has been demonstrated in patients with IBS whose primary complaints are abdominal pain and constipation.[18,19]

Many types of fiber supplements are available, some synthetic (eg, polycarbophil, methylcellulose) and others from natural sources (eg, bran, psyllium compounds). All types of fiber may cause increased bloating and gaseousness due to colonic metabolism of nondigestible fiber.

Because of its safety, a trial of fiber supplementation is advised in patients with IBS, especially those with constipation as the predominant symptom. The amount should be titrated to the symptoms, but 10 g of fiber per day is good starting dosage.

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Psychosocial therapy

Behavioral treatment may be considered for motivated patients who associate symptoms with stressors. Cognitive-behavioral treatment, interpersonal (psychodynamic) therapy, hypnosis, biofeedback, stress management and relaxation training, and family or group therapy are all reasonable options. They reduce anxiety levels, encourage health-promoting behaviors, increase patient responsibility and involvement in the treatment, and improve pain tolerance. Factors that favor a good response to psychotherapy include[20]:

- High patient motivation
- Diarrhea or pain as the predominant symptom
- IBS associated with overt psychiatric symptoms
- Intermittent pain exacerbated by stress.

Patients with constant abdominal pain respond poorly to psychotherapy or hypnotherapy.

TABLE 2

Symptom-oriented drug therapy in irritable bowel syndrome

PREDOMINANT SYMPTOM	GASTROINTESTINAL AGENTS TO TRY	ANTIDEPRESSANT DRUGS TO TRY
Diarrhea	Loperamide Diphenoxylate	Tricyclic antidepressants
Constipation	Osmotic laxatives Fiber supplementation	SSRIs (eg, sertraline) Serotonin 5-HT4 agonist (tegaserod*)
Pain, gas, bloating, urgency	Antispasmodics Anticholinergics	Tricyclic antidepressants SSRIs

*Currently under FDA review for use in treatment of constipation in patients with IBS

GASTROINTESTINAL DRUG THERAPY

Drug therapy for IBS symptoms should be minimal or avoided altogether because of the lifelong nature of the disorder and the lack of convincing therapeutic benefit. The difficulty in demonstrating therapeutic efficacy may in part be due to the heterogeneity of patients with IBS, the lack of disease markers, and high placebo response rates.[21]

Drug therapy for IBS symptoms: avoid, or use sparingly

The drug chosen depends on the patient's major symptoms (constipation, diarrhea, abdominal pain). Common strategies are to use dietary fiber for constipation, loperamide or diphenoxylate for diarrhea, and anticholinergic, antispasmodic agents, tricyclic antidepressants or serotonin reuptake inhibitors (SSRIs) for pain (TABLE 2).

Antidiarrheal agents

Loperamide (Imodium) has been shown to be beneficial in diarrhea-predominant IBS by slowing whole-gut transit and enhancing intestinal water and electrolyte absorption.[22] It does not require a prescription and is the antidiarrheal drug of choice. Diphenoxylate (Lomotil) can be given if loperamide is not effective.

Anticholinergic and antispasmodic agents

Anticholinergic and antispasmodic agents are the most frequently used drugs in the treatment of IBS. They may be beneficial in patients with postprandial abdominal pain, gas, bloating, and fecal urgency.

In a recent meta-analysis of randomized, controlled trials, 13 of 16 studies of smooth-muscle relaxants showed these agents to be efficacious in global or symptomatic improvement.[23] In fact, among all the pharmacologic agents, only smooth muscle relaxants consistently decreased abdominal pain, the most frequent and disabling symptom of IBS. However, the four agents (cimetropium, pinaverium, otilonium, and trimebutine) that consistently showed efficacy in high-quality trials are not yet approved for treatment of IBS in the United States. Data on the effectiveness of the antispasmodic dicyclomine (Bentyl) in IBS patients are limited.[24]

Common adverse effects of anticholinergic agents are dry mouth, dizziness, blurred vision, drowsiness, and tachycardia. Because of these effects and the intermittent nature of pain in IBS, we advise using such agents on an as-needed basis or in anticipation of stressors with known exacerbating effects.

Dosage. Hyoscyamine (Levsin) can be given for pain at a dose of 0.125 mg to 0.25 mg sublingually or by mouth three to four times daily, or as a sustained-release tablet 0.375 mg to 0.75 mg by mouth every 12 hours. A typical dosage for dicyclomine is 20 mg by mouth three or four times a day, or three to four times a day as needed.

ANTIDEPRESSANT THERAPY: OFTEN BENEFICIAL

Antidepressants are beneficial in patients with IBS and are often used in patients with chronic refractory symptoms. They are particularly helpful in patients with comorbid depressive and anxiety disorders. Antidepressants also have analgesic properties independent of their

psychotropic effects and may therefore be beneficial in patients with neuropathic pain.[25]

Tricyclic antidepressants and selective serotonin reuptake inhibitors (SSRIs) modulate visceral afferent activity from the gastrointestinal tract and may improve abdominal pain.[26] Tricyclics are helpful in IBS patients with predominant diarrhea,[27] possibly because of their constipating effect. Conversely, some SSRIs may cause diarrhea, so caution is advised before prescribing SSRIs in IBS patients with diarrhea as the predominant complaint.

Because antidepressants must be taken on a continuous basis, regardless of the type, they should be used in patients who suffer from frequent symptoms.

Tricyclic antidepressants. Improvement in neuropathic pain with tricyclic antidepressant therapy occurs at lower doses than are required for treatment of depression. Thus, low doses should be tried initially and titrated to pain control or tolerance. Because these drugs have a delayed onset of action, the initial low dosage should be given for 3 to 4 weeks before it is deemed insufficient and increased.

Frequently used antidepressants include amitriptyline (Elavil) 10 to 25 mg by mouth at bedtime, and imipramine (Tofranil) 25 to 50 mg by mouth at bedtime. The initial dose should be adjusted on the basis of the individual patient's tolerance and response.

SSRIs. Although SSRIs are increasingly preferred over tricyclic agents because of their low adverse effect profile, data regarding their use in IBS are limited.[23,26] As with tricyclic antidepressants, SSRI treatment for IBS should start with low doses; eg, paroxetine (Paxil) 20 mg by mouth daily, fluoxetine (Prozac) 20 mg by mouth daily, or sertraline (Zoloft) 50 mg by mouth daily.

Serotonin receptor agonists and antagonists

Serotonin (5-hydroxytryptamine or 5-HT) serves both as a neurotransmitter and as a paracrine signaling molecule in the bowel.[28] Serotonin is distributed throughout the gut, predominantly within enterochromaffin cells in the mucosal crypts and, to a lesser extent, within the nerve fibers of the myenteric and submucosal plexuses. The concentration of serotonin in the bowel is substantially greater than in the brain.[28] It is estimated that 95% of the body's serotonin is synthesized and stored in the enterochromaffin cells of the gut.[28] Thus, serotonin has become a primary focus of recent research.

Postprandial plasma levels of serotonin in IBS patients with diarrhea as the chief symptom are significantly higher than those in healthy controls.[29] Antagonists of serotonin type 5-HT3 receptors have been shown to increase colonic compliance, delay colonic transit, improve stool consistency, and increase thresholds for sensation and discomfort during distention of the rectum.[30]

Alosetron (Lotronex), a selective 5-HT3 receptor antagonist, was the only drug in its class approved for treatment of women for whom diarrhea is a predominant symptom. Alosetron was shown to produce statistically significant improvement in abdominal pain, stool consistency, frequency and urgency in female IBS patients,[31,32] though symptoms rapidly return if treatment is stopped.[32] However, alosetron was recently withdrawn from use because of reports of ischemic colitis.

Tegaserod is an amino guanidine-indole with selective and partial serotonin type 5-HT4 receptor agonist activity. Serotonin 5-HT4 agonists exert gastrointestinal stimulatory effects, partially by facilitation of enteric cholinergic transmission.[33] The medication is currently under review by the US Food and Drug Administration for the treatment of constipation in IBS patients. Tegaserod in doses of 25 to 100 mg twice a day accelerated transit time through the left colon in healthy people.[34] In a recent randomized, double-blind, placebo-controlled study of patients with IBS and constipation as the predominant symptom, tegaserod 4 mg/day or 12 mg/day significantly improved abdominal pain, bowel function, and general well-being.[35]

Antidepressants are often helpful in IBS

IBS patients with constipation as the chief symptom often have delayed small bowel transit or colonic transit, or both.[36] In a recent randomized, placebo controlled trial of a group of these patients, tegaserod 2 mg by mouth twice a day accelerated orocecal transit, mostly via shortened small bowel transit.[37] The most frequent adverse events were gastrointestinal: abdominal pain, diarrhea, dyspepsia, flatulence, or vomiting.

REFERENCES

1. **Mitchell CM, Drossman DA.** Survey of the AGA membership relating to the patients with functional gastrointestinal disorders. Gastroenterology 1987; 92:1282–1284.
2. **Talley NJ, Zinsmeiser AR, Van Dyke C, Melton LJ.** Epidemiology of colonic symptoms and the irritable bowel syndrome. Gastroenterology 1991; 101:927–934.
3. **Drossman DA, Li A, Andruzzi E, Temple RD, Talley NJ, Thompson WG.** US householders survey of functional gastrointestinal disorders. Prevalence, sociodemography, and health impact. Dig Dis Sci 1993; 38:1569–1580.
4. **Drossman DA, Whitehead WE, Camilleri M.** Irritable bowel syndrome: A technical review for practice guideline development. Gastroenterology 1997; 112:2120–2137.
5. **Sandler RS.** Epidemiology of irritable bowel syndrome in the United States. Gastroenterology 1990; 99:409–415.
6. **Hahn BA, Yan S, Strassels S.** Impact of irritable bowel syndrome on quality of life and resource use in the United States and United Kingdom. Digestion 1999; 60:77–81.
7. **Drossman DA.** Review article: An integrated approach to the irritable bowel syndrome. Aliment Pharmacol Ther 1999; 13 Suppl 2:3–14.
8. **Mertz H, Naliboff B, Munakata J, Niazi N, Mayer EA.** Altered rectal perception is a biological marker of patients with irritable bowel syndrome. Gastroenterology 1995; 109:40–52.
9. **Whitehead WE, Holtkotter B, Enck P, et al.** Tolerance for rectosigmoid distention in irritable bowel syndrome. Gastroenterology 1990; 98:1187–1192.
10. **Cook IJ, van Eeden A, Collins SM.** Patients with irritable bowel syndrome have greater pain tolerance than normal subjects. Gastroenterology 1987; 93:727–733.
11. **Lynn RB, Friedman LS.** Irritable bowel syndrome. N Engl J Med 1993; 329:1940–1945.
12. **Whorwell PJ, McCallem M, Creed FH, Roberts CT.** Non-colon features of irritable bowel syndrome and non-ulcer dyspepsia. Gut 1986; 27:37–40.
13. **Fass R, Fullerton S, Naliboff B, Hirsh T, Mayer EA.** Sexual dysfunction in women with the irritable bowel syndrome and non-ulcer dyspepsia. Digestion 1998; 59:79–85.
14. **Fass R, Fullerton S, Tung S, Mayer EA.** Sleep disturbances in clinic patients with functional bowel disorders. Am J Gastroenterol 2000; 95:1195–2000.
15. **Manning AP, Thompson WG, Heaton KW, Morris AF.** Towards positive diagnosis of the irritable bowel. Br Med J 1978; 2:653–654.
16. **Thompson WG, Longstreth GF, Drossman DA, Heaton KW, Irvine EJ, Muller-Lissner SA.** Functional bowel disorders and functional abdominal pain. (Rome II: A multinational consensus document on functional gastrointestinal disorders). Gut 1999; 45 Suppl 2:43–47.
17. **Drossman DA, Whitehead WE, Camilleri M.** Irritable bowel syndrome: A technical review for practice guideline development. Gastroenterology 1997; 112:2120–2137.
18. **Lucey MR, Clark ML, Lownes J, Dawson AM.** Is bran efficacious in irritable bowel syndrome? A double-blind placebo-controlled crossover study. Gut 1987; 28:221–225.
19. **Cook IJ, Irvine EJ, Campbell D, Shannon S, Reddy SN, Collins SM.** Effect of dietary fiber on symptoms and rectosigmoid motility in patients with irritable bowel syndrome. Gastroenterology 1990; 98:66–72.
20. **Camilleri M.** Review article: Clinical evidence to support current therapies of irritable bowel syndrome. Aliment Pharmacol Ther 1999; 13 Suppl 2:48–53.
21. **Klein KB.** Controlled treatment trials in the irritable bowel syndrome: A critique. Gastroenterology 1988; 95:232–241.
22. **Cann PA, Read NW, Holdsworth CD, Barends D.** Role of loperamide and placebo in management of irritable bowel syndrome. Dig Dis Sci 1984; 29:239–247.
23. **Jailwala J, Imperiale TF, Kroenke K.** Pharmacological treatment of the irritable bowel syndrome: A systemic review of randomized, controlled trials. Ann Intern Med 2000; 133:136–147.
24. **Page JG, Dirnberger GM.** Treatment of the irritable bowel syndrome with Bentyl (dicyclomine hydrochloride). J Clin Gastroenterol 1981; 3:153–156.
25. **Hameroff SR, Weiss JL, Lerman JC, et al.** Doxepin's effect on chronic pain and depression: A controlled study. J Clin Psychiatry 1984; 45:47–53.
26. **Clouse RE.** Antidepressants for functional gastrointestinal syndromes. Dig Dis Sci 1994; 39:2352–2363.
27. **Myren J, Lovland B, Larssen SE, Larsen S.** A double study of the effect of trimipramine in patients with the irritable bowel syndrome. Scand J Gastroenterol 1984; 19:835–843.
28. **Gershon MD.** Review article: Roles played by 5-hydroxytryptamine in the physiology of bowel. Aliment Pharmacol Ther 1999; 13 Suppl 2:15–30.
29. **Bearcroft CP, Perrett D, Farthing MJG.** Postprandial plasma 5-hydroxytryptamine in diarrhea predominant irritable bowel syndrome: A pilot study. Gut 1998; 42:42–46.
30. **Humphrey PP, Bountra C, Clayton N, Kozlowski K.** Review article: The therapeutic potential of 5-HT3 receptor antagonists in the treatment of irritable bowel syndrome. Aliment Pharmacol Ther 1999; 13 Suppl 2:31–38.
31. **Mangel AW, Northcutt AR.** Review article: The safety and efficacy of alosetron, a 5-HT3 receptor antagonist, in female irritable bowel syndrome patients. Aliment Pharmacol Ther 1999; 13 Suppl 2:77–82.
32. **Camilleri M, Northcutt AR, Kong S, Dukes G, McSorley D, Mangel AW.** Efficacy and safety of alosetron in women with irritable bowel syndrome: A randomized, placebo-controlled trial. Lancet 2000; 355:1035–1040.
33. **Wiseman LR, Faulds D.** Cisapride: An updated review of its pharmacology and therapeutic efficacy as a prokinetic agent in gastrointestinal motility disorders. Drugs 1994; 47:116–152.
34. **Appel S, Kumle A, Hubert M, Duvauchelle T.** First pharmacokinetic pharmacodynamic study in humans with a selective 5-hydroxytryptamine-4 receptor agonist. J Clin Pharmacol 1997; 37:229–237.
35. **Mueller-Lissner S, Fumagalli I, Bardhan K, et al.** Tegaserod, a 5-HT4 receptor agonist, relieves key symptoms of irritable bowel syndrome [abstract]. Gastroenterology 2000; 118:A175.
36. **Cann PA, Read NW, Brown C, Hobson N, Holdsworth CD.** Irritable bowel syndrome: Relationship of disorders in the transit of a single solid meal to symptom patterns. Gut 1983; 24:405–411.
37. **Prather CM, Camilleri M, Zinsmeister AR, McKinzie S, Thomforde G.** Tegaserod accelerates orocecal transit in patients with constipation-predominant irritable bowel syndrome. Gastroenterology 2000; 118:463–468.

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