Irritable bowel syndrome: Minimize testing, let symptoms guide treatment

Keith B. Holten, MD
University of Cincinnati College of Medicine, Cincinnati, Ohio

Practice recommendations

- For patients aged <50 years without alarm symptoms, diagnostic testing is unnecessary. Consider celiac sprue testing for patients with diarrhea **(C).**
- Treatment is indicated when both the patient with irritable bowel syndrome and the physician agree that quality of life has been diminished **(C).** The goal of therapy is to alleviate global IBS symptoms (abdominal discomfort, bloating, and altered bowel habits that are life-impacting) **(C).**
- Tegaserod, a $5HT_4$ receptor agonist, is more effective than placebo at relieving global IBS symptoms in women with constipation **(A).** Its effectiveness in men is unknown.
- Alosetron, a $5HT_3$ receptor antagonist, is more effective than placebo at relieving global IBS symptoms in women with diarrhea **(A).**
- Behavior therapy—relaxation therapy, hypnotherapy, or cognitive therapy—is more effective than placebo at relieving individual symptoms, but no data are available for quality-of-life improvement **(B).**

Correspondence: Keith B. Holten, MD, Clinton Memorial Hospital / University of Cincinnati Family Practice Residency, 825 W. Locust St., Wilmington, OH, 45177. E-mail: keholtenmd@cmhregional.com.

An extensive and expensive evaluation for irritable bowel syndrome (IBS) can be avoided if your patient is aged <50 years and is not experiencing alarm symptoms (hematochezia, 10 lbs weight loss, fever, anemia, nocturnal or severe diarrhea), has not recently taken antibiotics, and has no family history of colon cancer. An algorithm (**Figure**) indicates when work-up is needed and what it should entail.

Newer medications that act on 5HT receptors have proven effective in improving quality of life (global symptom reduction). Evidence supports the use of several traditional medications to reduce individual symptoms of IBS, but not for global symptom reduction.

WHO GETS IRRITABLE BOWEL SYNDROME?

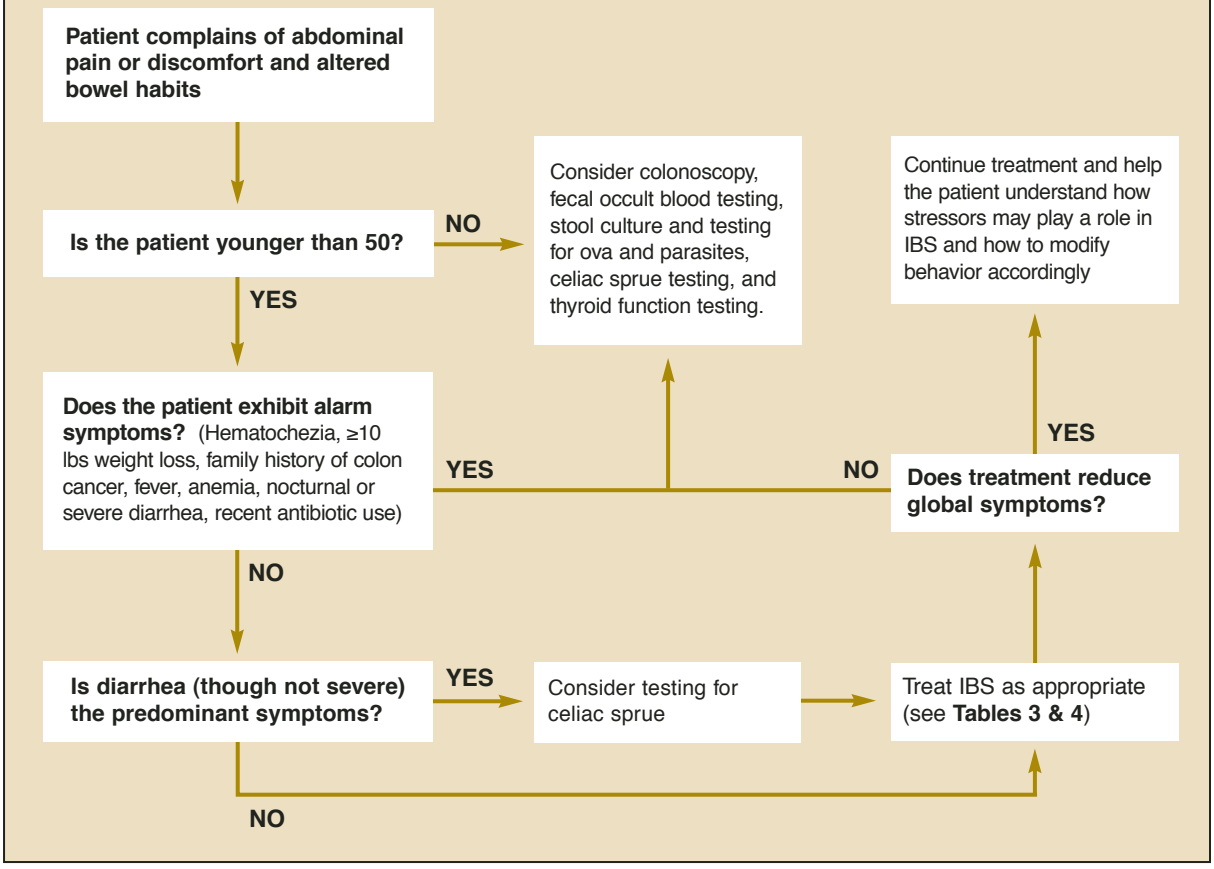
Ten percent to 15% of the North American population has IBS, and twice as many women as men have it.[1] Symptoms usually begin before the age of 35 years, and many patients can trace their symptoms back to childhood.[2] Onset in the elderly is rare.[3] The disorder is responsible for approximately 50% of referrals to gastroenterologists.[4]

The company IBS keeps

Comorbid psychiatric illness is common with IBS, but few patients seek psychiatric care.[5] Depression, anxiety, and somatoform disorders are seen in 94% of patients with IBS. IBS is common in patients with chronic fatigue

FIGURE

Evaluating possible irritable bowel syndrome



syndrome (51%), fibromyalgia (49%), temporomandibular joint syndrome (64%), and chronic pelvic pain (50%).[6] IBS often follows stressful life events,[5,7,8] such as a death in the family or divorce. It tends to be chronic, intermittent, and relapsing.[3]

The symptoms of IBS can overlap with those of other illnesses, including thyroid dysfunction (diarrhea or constipation), functional dyspepsia (abdominal pain), Crohn's disease or ulcerative colitis (diarrhea, abdominal pain), celiac sprue (diarrhea), polyps and cancers (constipation or abdominal pain), and infectious diarrhea.

Elusive physiologic mechanism

Several physiologic mechanisms have been proposed for IBS symptoms: altered gut reactivity in response to luminal stimuli, hypersensitive gut with enhanced pain response, and altered brain-gut biochemical axis.[9] Though the symptoms of irritable bowel syndrome appear to have a physiologic basis, there are no structural or biochemical markers for the disease.

USE SYMPTOM-BASED CRITERIA FOR DIAGNOSIS

Consider a diagnosis of IBS when a patient complains of abdominal discomfort and altered bowel habits. In the absence of a structural or biochemical marker, IBS must be diagnosed according to symptom-based criteria—such as Manning, Rome I, or Rome II—which have been

TABLE 1

Symptom-based criteria for irritable bowel syndrome

Symptom-based criteria	Symptoms	Sn	Sp	PV+
Manning[4,10,13,14]	• Abdominal pain • Pain relief with bowel movement • More frequent stools with pain • Looser stools with pain • Mucus in stools • Feeling of incomplete evacuation	42%–90%	70%–100%	74%
Rome I[4,10,13]	• >3 months of continuous or recurrent abdominal pain relieved with defecation or associated with change in stool consistency • plus: >2 of the following on 25% of days – altered stool frequency – altered stool form – altered stool passage – passage of mucus – bloating or abdominal distention	65%–84%	100%	69%–100%
Rome II[11–13]	• Abdominal discomfort or pain for at least 12 weeks (not necessarily consecutive) in the preceding 12 months, and having 2 of the 3 following features: – relieved with defecation – onset associated with a change in frequency of stool – onset associated with a change in form (appearance) of stool **Supportive symptoms** Fewer than 3 bowel movements per week More than 3 bowel movements per day Hard or lumpy stools	49%–65%*	100%*	69%–100%*

*Found to have similar sensitivity and specificity to Rome I.[14]
Sn, sensitivity; Sp, specificity; PV+, positive predictive value

developed for research and epidemiologic purposes. Though their clinical utility remains unproven, these criteria (delineated in **Table 1)** are the crux of clinical diagnosis for IBS.[4,10–14] Subtypes of IBS have been described (diarrhea-predominant IBS or constipation-predominant IBS), but they are not diagnostically useful, since the treatment goal is improved quality of life.

Dubious value of diagnostic tests

The literature regarding the value of diagnostic testing for IBS is controversial. Symptom-based criteria have varied in many studies, as have the criteria used to enroll patients and the measured outcomes of treatment (reduction in abdominal pain, in diarrhea, or in constipation, or improvement in quality of life). Because of

these discrepancies, it is difficult to apply the literature clinically. Of the 6 landmark studies that considered the value of diagnostic testing for IBS patients,[15–20] only 2 compared IBS patients with groups of healthy controls.[17,19]

Test results yield little. Most research in this area has compared the prevalence of specific illnesses in the general population with the yield of positive test results for these illnesses among persons meeting the symptom-based diagnostic criteria for IBS.

Two studies[15,16] determined the incidence of abnormal test results in patients who met the Manning or Rome I criteria for IBS. In these studies, most diagnostic tests yielded positive results in 2% (range, 0%–8.2%) of patients or less, except for thyroid and lactose intolerance testing. That is equivalent to the incidence in the general population. The prevalence of thyroid disorders and lactose malabsorption was higher in IBS patients (6% and 22%–26%, respectively), but prevalence in the general population is similarly higher (5%–9% and 25%). Based on these results, testing for thyroid disease or lactose malabsorption is indicated only for patients exhibiting symptoms of these disorders (fatigue/weight change or diarrhea related to diertary intake of dairy products, respectively).

An exception. Some clinicians propose that diagnostic testing for patients with IBS symptoms should be driven by the pretest probability of organic disease (prevalence) compared with the general population. Cash[21] found the pretest probability of inflammatory bowel disease, colorectal cancer, and infectious diarrhea is less than 1% among IBS patients without alarm symptoms (**Table 2**). He demonstrated that patients with IBS had a 5% pretest probability of celiac sprue compared with healthy patients (<1% prevalence). Therefore, testing for celiac sprue (eg, complete blood count, anti-endomysial antibody, and antigliadin antibody) may be considered for patients with diarrhea.[6,21,22] Sigmoidoscopy,[15,17] rectal biopsy,[17] and abdominal ultrasound[18] have low positive yield in patients meeting the diagnostic criteria for IBS.

How to proceed

Those under 50 years of age who have no alarm symptoms can forgo further testing. Testing for celiac sprue and lactose malabsorption might be considered for patients with diarrhea that improves or worsens with change in diet (strength of recommendation [SOR]: **C**).

THRESHOLD FOR TREATMENT

Treatment for IBS is indicated when both patient and physician believe global symptoms (abdominal discomfort, bloating, altered bowel habits) have diminished the quality of life (SOR: **C**). The goal of treatment is to alleviate all IBS symptoms (SOR: **C**). Treating altered bowel habits (constipation, diarrhea, and fecal urgency) without addressing other IBS symptoms (eg, abdominal pain) is inferior treatment.[23,24]

Treatment options for IBS

Treatments for IBS include medications, behavior therapy, and complimentary and alternative therapies. Medications traditionally prescribed include bulking agents, anticholinergics/antispasmodics, antidiarrheals, and antidepressants. A $5HT_3$ receptor antagonist and a $5HT_4$ receptor partial agonist are now available. **Table 3** summarizes the traditional treatments in terms of efficacy, strength of recommendations, and outcomes measured. Alternative and complimentary therapies appear in **Table 4.**

As Brandt[24] has noted, the evidence for treatment effectiveness is difficult to review and summarize, because the quality of studies has been poor. Most studies did not use healthy control groups, and the numbers of participants were small. Many studies did not use blinded placebo groups. Outcomes measured varied among the studies, with most of them measuring reductions of individual bowel symptoms

TABLE 2

Probability of organic disease in irritable bowel syndrome patients

Disease	Pretest probability–IBS patients (%)	Prevalence–general population (%)	Comments
Colitis/inflammatory inflammatory bowel disease	0.51–0.98	0.3–1.2	Structural colon lesions were detected with barium enema, colonscopy, sigmoidoscopy
Colon cancer	0–0.51	4–6	Structural colon lesions were detected with barium enema, colonoscopy, sigmoidoscopy
Celiac disease	4.67	0.25–0.5	Note: celiac disease prevalence higher than in general population.
Gastrointestinal infection	0–1.7	N/A	
Thyroid dysfunction	6	5–9	Prevalence high in both groups
Lactose malabsorption	22–26	25	Prevalence high in both groups

Adapted from: Cash BD, Schonfeld P, Chey WD. The utility of diagnostic tests in irritable bowel syndrome patients: a systematic review. *Am J Gastroenterol* 2002; 97:2812–2819.
Results are from multiple studies: n=125–306.

(eg, diarrhea or constipation). Quality-of-life tools were used in other studies to measure reduction in global IBS symptoms (eg, IBS Quality of Life[25]). Because of these discrepancies, there is no sound evidence for traditional therapies.

Medications

Strength of recommendation: A. The recently approved $5HT_4$ receptor agonist tegaserod (Zelnorm) is more effective than placebo at relieving global symptoms in women with constipation (number needed to treat [NNT]=3.9–17).[26–30] Diarrhea can be a serious side effect.

The $5HT_3$ receptor antagonist alosetron (Lotronex) is more effective than placebo at relieving global IBS symptoms in women with diarrhea (NNT=2.5–8.3).[31–35] Severe constipation can be an adverse effect. The prescribing of alosetron is currently restricted to physicians who participate in the manufacturer's risk management program.

In addition to these serotoninergic agents, others in this class are being developed and undergoing clinical trials. The knowledge being gained about 5HT receptors may revolutionize the care of patients with IBS.

Strength of recommendation: B. Tricyclic antidepressants are no more effective than placebo at relieving global IBS symptoms, but they do decrease abdominal pain (NNT=3.2–5).[36–39]

Loperamide is no more effective than placebo at relieving IBS global symptoms, but it may be used to treat diarrhea (NNT=2.3–5).[31,40–42]

TABLE 3

Treatments for irritable bowel syndrome

Treatment	Efficacy (NNT)	SOR (studies)	Outcomes measured	Comments
5HT$_4$ receptor agonist (tegaserod)[23,24,26–30]	More effective than placebo at relieving global IBS symptoms in women with constipation (3.9–17)	**A** (4)	Global IBS symptoms, individual IBS symptoms	83%–100% of study participants were women with IBS and constipation. Rome I and II criteria for entry. May cause diarrhea
5HT$_4$ receptor agonist (alosetron)[23,24,26–35]	More effective than placebo at relieving global IBS symptoms in women with diarrhea (2.5–8.3)	**A** (4)	Global IBS symptoms, individual IBS symptoms, adverse events	82%–93% of study participants were women. Rome I and II criteria for entry. May cause severe constipation; restricted use
Tricylic anti-depressants (trimipramine, desipramine)[23,24,36–39]	Reduces abdominal pain. No more effective than placebo at relieving gloal IBS symptoms (3.2–5)	**B** (6)	GI symptoms	May cause constipation; no studies done with SSRIs
Loperamide[23,24,36–39]	Relieves diarrhea. No more effective than placebo at relieving global IBS symptoms (3.2–5)	**B** (3)	Global IBS symptoms, diarrhea	Constipation or paralytic ileus can occur
Bulking agents (corn fiber, wheat bran, psyllium, ispaghula husks, calcium poly-cabophil)[23,24,31,40–42]	Improves constipation. No more effective than placebo in studies considering global symptom improvement (2.2–8.6)	**B** (13)	GI symptoms, global IBS symptoms	May increase bloating. All studies small numbers of patients
Anti-spasmodics (hyoscyamine dicyclomine)[23,24,26–30]	No evidence on improvement of global IBS symptoms (5.9)	**B** (3)	Individual IBS and global symptoms	Studies were short, small numbers, inconsistent effectiveness. Could worsen constipation; 15 additional studies done on drugs not available in the US
Behavioral therapies (hypno-therapy, relaxation therapy, psycho-therapy, bio-feedback)[23.24,44, 52–57]	More effective than placebo at relieving individuals IBS sypmtoms (1.4–1.9)	**B** (16)	GI symptoms, psychological symptoms	None measures global IBS symptom improvement. Small numbers of patients
SSRI antidepressants (paroxtetine, fluoxetine)[23,24, 50–51]	Improved quality of life, decreased abdominal pain	**B** (16)	Abdominal	One study severe IBS, other study only 10 participants quality of life

SOR, strength of recommendation; IBS, irritable bowel syndrome; GI, gastrointestinal; SSRI, selective serotonin reuptake inhibitor. For an explanation of SORs, see page 954.

TABLE 4

Complementary and alternative treatments for irritable bowel syndrome

Treatment	Efficacy	SOR	Outcomes measured	Comments
Neomycin[20]	Treatment for 1 week improved symptoms of abdominal pain, diarrhea, and constipation	**A**	Abdominal pain, diarrhea, or constipation	Studies measuring global symptom improvement lacking
Peppermint oil[31,48–49]	Some demonstrated improvement in abdominal pain	**B**	Individual IBS symptoms	Studies measuring global symptom improvement lacking
Guar gum[44]	Improved abdominal pain and bowel alterations	**B**	Study compared fiber to guar gum—equal affect on abdominal pain. Gum was better tolerated	No placebo-controlled trials
Probiotics[48] (lactobacillus)	Improvement of abdominal pain and flatulence	**C**	Abdominal pain, flatulence	Two studies with small numbers
Elimination diets[48]	Improvement of diarrhea	**C**	Diarrhea	Milk, wheat, eggs eliminated; 15%–71% improvement of diarrhea
Lactose and fructose avoidance[48]	Conflicting evidence results	**D**		No controlled studies available
Pancreatic enzymes[48]	No evidence	**D**		Evidence lacking
Ginger[48]	No evidence	**D**		No studies

Bulking agents (such as calcium polycarbophil or psyllium) are no more effective than placebo at relieving IBS global symptoms, but they may decrease constipation (NNT=2.2–8.6).[31,36,43–47]

Peppermint oil may be helpful for abdominal pain, but global symptom reduction has not been demonstrated.[31,48–49] Only a few studies have looked at the use of antispasmodic agents for IBS. They are of poor quality and used small numbers with no placebo controls.[23,31,36,43]

Strength of recommendation: C. There are limited studies evaluating the selective serotonin reuptake inhibitors (SSRIs) fluoxetine and paroxetine. Paroxetine was shown in 1 study to improve quality of life.[50] Fluoxetine reduced abdominal pain, but did not improve quality of life.[51]

Behavioral and complementary/alternative therapies

Relaxation therapy, hypnotherapy, and cognitive therapy are effective at relieving individual IBS symptoms, but have not been shown to reduce global IBS symptoms (SOR: **B**).[52–57] Other alternative therapies (eg, guar gum[44] [SOR: **B**], ginger[48] [SOR: **B**], and pancreatic enzymes[48] [SOR: **C**]) have been studied, but high-quality

Methods used to develop this article

The position statement of the American College of Gastroenterology on the management of IBS[23] and Brandt's systematic review of this subject[24] were the starting points for this review. The majority of the references from these sources were reviewed and a Medline search was completed to identify new evidence. The Oxford Centre for Evidence-Based Medicine grades of recommendations were applied to this evidence, a care algorithm was created, summary tables were developed, and numbers needed to treat were calculated.

studies considering global improvement have not been published.

PROMOTE SELF-AWARENESS

Quality-of-life assessment should be done routinely in the care of IBS patients. Provide support, empathy, and basic behavior modification tools. Educate patients and their families on the theoretical biochemical basis of this illness, and help them connect symptoms with stressors, to facilitate lifestyle modification.

REFERENCES

1. Saito YA, Schoenfeld P, Locke R. The epidemiology of irritable bowel syndrome in North America: A systematic review. *Am J Gastrenterol* 2002; 97:1910–1915.
2. Talley NJ, Gabriel SE, Harmsen WS, Zinsmeister AR, Evans RW. Medical costs in community subjects with irritable bowel syndrome. *Gastroenterology* 1995; 109:1736–1741.
3. Maxwell PR, Mendall MA, Kumar D. Irritable bowel syndrome. *Lancet* 1997; 350:1691–1695.
4. Fass R, Longstreth GF, Pimental M, et al. Evidence- and consensus-based practice guidelines for the diagnosis of irritable bowel syndrome. *Arch Intern Med* 2001; 161:2081–2088.
5. Goldberg J, Davidson P. A biopsychosocial understanding of the irritable bowel syndrome: a review. *Can J Psychiatry* 1997; 42:835–840.
6. Whitehead WE, Palsson O, Jones KR. Systematic review of the comorbidity of irritable bowel syndrome with other disorders: What are the causes and implications? *Gastroenterology* 2002; 122:1140–1156.
7. Olden KW, Drossman DA. Psychologic and psychiatric aspects of gastrointestinal disease. *Med Clin North Am* 2000; 84:1313–1327.
8. Aaron LA, Burke MM, Buchwald D. Overlapping conditions among patients with chronic fatigue syndrome, fibromyalgia, and temporomandibular disorder. *Arch Intern Med* 2000; 160:221–227.
9. Camilleri M and Prather CM. The irritable bowel syndrome: mechanisms and a practical approach to management. *Ann Internal Med* 1992; 116:1001–1008.
10. Paterson WG, Thompson WG, Vanner SJ, et al. Recommendations for the management of irritable bowel syndrome in family practice. *JAMC* 1999; 161:154–160.
11. Olden KW. Diagnosis of irritable bowel syndrome. *Gastroenterology* 2002; 122:1701–1714.
12. Tosetti C, Stanghellini V, Corinaldesi R. The Rome II criteria for patients with functional gastroduodenal disorders. *J Clin Gastroenterol* 2003; 37:92–93.
13. Chey WD, Olden K, Carter E, Boyle J, Drossman D, Chang L. Utility of the Rome I and Rome II criteria for irritable bowel syndrome in US women. *Am J Gastroenterol* 2002; 97:2803–2811.
14. Vanner SJ, Depew WT, Paterson WG, et al. Predictive value of the Rome criteria for diagnosing the irritable bowel syndrome. *Am J Gastroenterol* 1999; 94:2912–2917.
15. Hamm LR, Sorrells SC, Harding JP, et al. Additional investigations fail to alter the diagnosis of irritable bowel syndrome in subjects fulfilling the Rome criteria. *Am J Gastroenterol* 1999; 94:1279–1282.
16. Tolliver BA, Herrara JL, DiPalma JA. Evaluation of patients who meet clinical criteria for irritable bowel syndrome. *Am J Gastroenterol* 1994; 89:176–178.
17. MacIntosh DG, Thompson WG, Patel DP, Barr R, Guindi M. Is rectal biopsy necessary in irritable bowel syndrome? *Am J Gastroenterol* 1992; 87:1407–1409.
18. Francis CY, Duffy JN, Whorwell PJ, Martin DF. Does routine ultrasound enhance diagnostic accuracy in irritable bowel syndrome? *Am J Gastroenterol* 1996; 91:1348–1350.
19. Sanders DS, Carter MJ, Hurlstone DP, et al. Association of adult celiac disease with irritable bowel syndrome: a case-control study in patients fulfilling Rome II criteria referred to secondary care. *Lancet* 2001; 358:1504–1508.
20. Pimental M, Chow EJ, Lin HC. Normalization of lactulose breath testing correlates with symptom improvement in irritable bowel syndrome; a double blind, randomized, placebo-controlled trial. *Am J Gastroenterol* 2003; 98:412–419.
21. Cash BD, Schonfeld P, Chey WD. The utility of diagnostic tests in irritable bowel syndrome patients: a systematic review. *Am J Gastroenterol* 2002; 97:2812–2819.
22. O'Leary CO, Wieneke P, Buckley S, et al. Celiac disease and irritable bowel-type symptoms. *Am J Gastroenterol* 2002; 97:1463–1467.
23. American College of Gastroenterology Functional Gastrointestinal Disorders Task Force. Evidence-based position statement on the management of irritable bowel syndrome in North America. *Am J Gastrenterol* 2002; 97:s1–s5.
24. Brandt LJ, Bjorkman D, Fennerty MB, Locke GR, Olden K, et al. Systematic review on the management of irritable bowel syndrome in north America. *Am J Gastroenterol* 2002; 97:s7–s26.
25. Drossman DA, Patrick DL, Whitehead WE, NE, et al. Further validation of the IBS-QOL: a disease-specific quality-of-life questionnaire. *Am J Gastroenterol* 2000; 95:999–1007.
26. Jones BW, Moore DJ, Robinson SM, Song F. A systematic

review of tegaserod for the treatment of irritable bowel syndrome. *J Clin Pharm Therapeutics* 2002; 27:343–352.

27. Novick J, Miner P, Krause R, et al. A randomized, double-blind, placebo-controlled trial of tegaserod in female patients suffering from irritable bowel syndrome with constipation. *Aliment Pharmacol Ther* 2002; 16:1877–1888.
28. Muller-Lissner SA, Fumagalli I, Bardhan KD, et al. Tegaserod, a 5-HT(4) receptor partial agonist, relieves symptoms in irritable bowel syndrome patients with abdominal pain, bloating and constipation. *Aliment Pharmacol Ther* 2001; 15:1655–1666.
29. Kellow J, Lee OY, Chang FY, et al. An Asia-Pacific, double blind, placebo controlled, randomised study to evaluate the efficacy, safety, and tolerability of tegaserod in patients with irritable bowel syndrome. *Gut* 2003; 52:671–676.
30. Jones RH, Holtmann G, Rodrigo L, Ehsanullah, Crompton PM, Jacques LA, Mills JG. Alosetron relieves pain and improves bowel function compared with mebeverine in female nonconstipated irritable bowel syndrome patients. *Aliment Pharmacol Ther* 1999; 13:1419–1427.
31. Jailwala J, Imperiale TF, Kroeneke K. Pharmacologic treatment of the irritable bowel syndrome: A systematic review of randomized, controlled trials. *Ann Intern Med* 2000; 133:136–147.
32. Cremonini F, Delgado-Aros S, Camilleri M. Efficacy of alosetron in irritable bowel syndrome: a meta-analysis of randomized controlled trials. *Neurogastroenterol Motil* 2002; 15:79–86.
33. Camilleri M, Northcutt AR, Kong S, Dukes GE, McSorley D, Mangel AW. Efficacy and safety of alosetron in women with irritable bowel syndrome: a randomised, placebo-controlled trial. *Lancet* 2000; 355:1035–1040.
34. Camilleri M, Mayer EA, Drossman DA, et al. Improvement in pain and bowel function in female irritable bowel patients with alosetron, a 5-HT3 receptor antagonist. *Aliment Pharmacol Ther* 1999; 13:1149–1159.
35. Lembo T, Wright RA, Bagby B, et al. Lotronex Investigator Team. Alosetron controls bowel urgency and provides global symptom improvement in women with diarrhea-predominant irritable bowel syndrome. *Am J Gastroenterol* 2001; 96:2662–2670.
36. Akehurst R, Kaltenthaler E. Treatment of irritable bowel syndrome: a review of randomized control trials. *Gut* 2001; 48:272–282.
37. Jackson JL, O'Malley PG, Tomkins G, Balden E, Santoro J, Kroeneke K. Treatment of functional gastrointestinal disorders with antidepressant medications: a meta-analysis. *Am J Med* 2000; 108:65–72.
38. Myren J, Lovland B, Larssen SE, Larsen S. A double-blind study of the effect of trimipramine in patients with the irritable bowel syndrome. *Scand J Gastroenterol* 1984; 19:835–843.
39. Greenbaum DS, Mayle JE, Vanegeren LE, et al. Effects of desipramine on irritable bowel syndrome compared with atropine and placebo. *Dig Dis Sci* 1987; 32:257–266.
40. Cann PA, Read NW, Holdsworth CD, Barends D. Role of loperamide and placebo in management of irritable bowel syndrome (IBS). *Dig Dis Sci* 1984; 29:239–247.
41. Hovdenak N. Loperamide treatment of the irritable bowel syndrome. *Scand J Gastroenterol Suppl* 1987; 130:81–84.
42. Efskind PS, Bernklev T, Vatn MH. A double-blind placebo-controlled trial with loperamide in irritable bowel syndrome. *Scand J Gastroenterol* 1996; 31:463–468.
43. Ritchie JA, Truelove SC. Treatment of irritable bowel syndrome with lorazepam, hyoscine butylbromide, and ispaghula husk. *Br Med J* 1979; 1:376–378.
44. Parisi GC, Zilli M, Miani MP, E, et al. High-fiber diet supplementation in patients with irritable bowel syndrome. A multi-center, randomized, open trial comparison between wheat bran diet and partially hydrolyzed guar gum. *Dig Dis Sci* 2002; 47:1697–1704.
45. Golechha AC, Chadda VS, Chadda S, Sharma SK, Mishra SN. Role of ispaghula husk in the management of irritable bowel syndrome (A randomized double-blind crossover study). *JAPI* 1982; 30:353–354.
46. Arthurs Y and Fielding JF. Double blind trial of ispaghula/poloxamer in the irritable bowel syndrome. *BMJ* 1983; 76:253.
47. Jalihal A and Kurian G. Ispaghula therapy in irritable bowel syndrome: Improvement in overall well-being is related to reduction in bowel dissatisfaction. *J Gastroenterol Hep* 1990; 5:507–513.
48. Spanier JA, Howden CW, Jones MP. A systematic review of alternative therapies in irritable bowel syndrome. *Arch Intern Med* 2003; 163:265–274.
49. Pittler MH, Ernst E. Peppermint Oil for irritable bowel syndrome: A critical review and meta-analysis. *Am J Gastroenterol* 1998; 93:1131–1135.
50. Creed F, Fernandes L, Guthrie E, et al. The cost-effectiveness of psychotherapy and paroxetine for severe irritable bowel syndrome. *Gastroenterology* 2003; 124:303–317.
51. Kuiken SD, Tytgat GNJ, Boeckxstaens GEE. The selective serotonin reuptake inhibitor fluoxetine does not change rectal sensitivity and symptoms in patients with irritable bowel syndrome: A double blind, randomized, placebo-controlled study. *Clin Gastroenterol Hepatol* 2003; 1:219–228.
52. Heymann-Monnikes I, Arnold R, Florin I, et al. 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; 95:981–994.
53. Talley NJ, Owen BK, Boyce P, Paterson K. Psychological treatments for irritable bowel syndrome: A critique of controlled treatment trials. *Am J Gastroenterol* 1996; 91:277–286.
54. Svedlund J, Sjodin I, Ottoson JO, Dotevall G. Controlled study of psychotherapy in irritable bowel syndrome. *Lancet* 1983; 2:589–592.
55. Greene B and Blanchard EB. Cognitive therapy for irritable bowel syndrome. *J Consulting Clinic Psychology* 1994; 62:576–582.
56. Guthrie E, Creed F, Dawson D, Tomenson B. A ramdomized controlled trial of psychotherapy in patients with refractory irritable bowel syndrome. *B J Psychiatry* 1993; 163:315–321.
57. Heymann-Monnikes I, Arnold R, Florin I, Herda C, Melfsen S, Monnikes H. 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; 95:981–994.