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SUPPLEMENT

An Evidence-Based Systematic Review on the Management of Irritable Bowel Syndrome

American College of Gastroenterology Task Force on IBS

ACG INSTITUTE FOR CLINICAL RESEARCH AND EDUCATION

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American College of Gastroenterology Task Force on Irritable Bowel Syndrome

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An Evidence-Based Systematic Review on the Management of Irritable Bowel Syndrome

SECTION 1

SECTION 2

AN EVIDENCE-BASED SYSTEMATIC REVIEW ON THE MANAGEMENT OF IRRITABLE BOWEL SYNDROME

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An Evidence-Based Position Statement on the Management of Irritable Bowel Syndrome

American College of Gastroenterology IBS Task Force

Irritable bowel syndrome (IBS) is a common disorder characterized by abdominal pain and altered bowel habit for at least 3 months. With this publication, an American College of Gastroenterology Task Force updates the 2002 Monograph on IBS in light of new data. A series of systematic reviews were performed to evaluate the diagnostic yield of investigations and the efficacy of treatments for IBS. The Task Force recommends that further investigations are unnecessary in young patients without alarm features with the exception of celiac sprue serology, which may be of benefit in some patients. Further investigation such as colonoscopy is recommended in those over 50 years of age and in patients with alarm features. Trials suggest psyllium fiber, certain antispasmodics, and peppermint oil are effective in IBS patients although the quality of the evidence is poor. Evidence suggests that some probiotics may be effective in reducing overall IBS symptoms but more data are needed. Antidiarrheals reduce the frequency of stools but do not affect the overall symptoms of IBS. $5HT_3$ antagonists are efficacious in IBS patients with diarrhea and the quality of evidence is good. Patients need to be carefully selected, however, because of the risk of ischemic colitis. $5HT_4$ agonists are modestly effective in IBS patients with constipation and the quality of evidence is good although the possible risk of cardiovascular events associated with these agents may limit their utility. Tricyclic antidepressants and selective serotonin reuptake inhibitors have been shown to be effective in IBS patients of all subtypes. The trials generally are of good quality but the limited number of patients included in trials implies that further evidence could change the confidence in the estimate of effect and therefore the quality of evidence was graded as moderate. Nonabsorbable antibiotics are effective particularly in diarrhea-predominant IBS and selective C-2 chloride channel activators are efficacious in constipation-predominant IBS with a moderate quality of evidence. Psychological therapies may also provide benefit to IBS patients although the quality of evidence is poor.

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Section 1 Evidence-based position statement on the management of irritable bowel syndrome

American College of Gastroenterology IBS Task Force

IBS is characterized by abdominal discomfort associated with altered bowel function; structural and biochemical abnormalities are absent. The pathophysiology of IBS is multifactorial and of intense recent interest, largely because of the possibility of developing targeted therapies. As IBS is one of the most common disorders managed by gastroenterologists and primary care physicians, this monograph was developed to educate physicians about its epidemiology, diagnostic approach, and treatments. The American College of Gastroenterology (ACG) IBS Task Force updated the 2002 monograph because new evidence has emerged on the benefit and risks of drugs used for IBS. Furthermore, new drugs also have been developed and the evidence for efficacy of these drugs needed to be assessed. To critically evaluate the rapidly expanding research about IBS, a series of systematic reviews were performed. Standard criteria for systematic reviews were met, including comprehensive literature searching, use of prespecified study selection criteria, and use of a standardized and transparent process to extract and analyze data from studies. Evidence-based statements were developed from these data by the entire ACG IBS Task Force. Recommendations were graded using a formalized system that quantifies the strength of evidence. Each recommendation was classified as strong (grade 1) or weak (grade 2) and the strength of evidence classified as strong (level A), moderate (level B), or weak (level C). Recommendations in this position statement may be cross-referenced with the supporting evidence in the accompanying article, "An Evidenced Based Review on the Management of Irritable Bowel Syndrome".

Irritable bowel syndrome: methodology for systematic reviews, levels of evidence and grading of recommendations (see Section 2.1).

The burden of illness of irritable bowel syndrome (see Section 2.2)

IBS is a prevalent and expensive condition that is associated with a significantly impaired health-related quality of life (HRQOL) and reduced work productivity. Based on strict criteria, 7–10%

of people have IBS worldwide. Community-based data indicate that diarrhea-predominant IBS (IBS-D) and mixed IBS (IBS-M) subtypes are more prevalent than constipation-predominant IBS (IBS-C), and that switching among subtype groups may occur. IBS is 1.5 times more common in women than in men, is more common in lower socioeconomic groups, and is more commonly diagnosed in patients younger than 50 years of age. Patients with IBS visit the doctor more frequently, use more diagnostic tests, consume more medications, miss more workdays, have lower work productivity, are hospitalized more frequently, and consume more overall direct costs than patients without IBS. Resource utilization is highest in patients with severe symptoms, and poor HRQOL. Treatment decisions should be tailored to the severity of each patient's symptoms and HRQOL decrement.

Prevalence estimates of IBS range from 1% to more than 20%. When limited to unselected population-based studies, the pooled prevalence of IBS in North America is 7%. Community-based data indicate that IBS-D and IBS-M subtypes are more prevalent than IBS-C, and that switching may occur among subtype groups. IBS is 1.5 times more common in women than in men, although IBS is not simply a disorder of women. In fact, IBS is now recognized to be a key component of the Gulf War Syndrome, a multi-symptom complex affecting soldiers (a predominantly male population) deployed in the 1991 Gulf War. IBS is diagnosed more commonly in patients under the age of 50 years than in patients older than 50 years. There is a graded decrease in IBS prevalence with increasing income.

Patients with IBS have a lower HRQOL compared with non-IBS cohorts. It is possible that patients with IBS develop HRQOL decrements due to their disease, and also possible that some patients with diminished HRQOL subsequently develop IBS. Although the precise directionality of this relationship may vary from patient to patient, it is clear that IBS is strongly related to low HRQOL, and vice versa. The HRQOL decrement can, in some cases, be so severe as to increase the risk of suicidal behavior. Because HRQOL decrements are common in IBS, we recommend that clinicians perform routine screening for diminished HRQOL in their IBS patients. Treatment should be initiated when the symptoms of IBS are found to reduce functional status and diminish overall HRQOL. Furthermore, clinicians should remain wary of potential suicidal behavior in patients with severe IBS symptoms, and should initiate timely interventions if suicide indicators are identified.

Patients with IBS consume a disproportionate amount of resources. IBS care consumes over $20 billion in both direct and indirect expenditures. Moreover, patients with IBS consume over 50% more health care resources than matched controls without IBS. Resource utilization in IBS is driven partly by the presence of comorbid somatization—a trait found in up to one-third of IBS patients that is characterized by the propensity to overinterpret normal physiologic processes. There is a highly significant relationship between levels of somatization and the amount of diagnostic testing in IBS, suggesting that providers should remain alert for signs of somatization in IBS, and aggressively treat or refer somatization patients to an experienced specialist rather than performing potentially unnecessary diagnostic tests.

In addition to direct costs of care, IBS patients engender significant indirect costs of care as a consequence of both missing work and suffering impaired work performance while on the job. Compared with IBS patients who exhibit normal work productivity, patients with impaired productivity have more extraintestinal comorbidities and more disease-specific fears and concerns. In contrast, the specific profile of individual bowel symptoms does not undermine work productivity, suggesting that enhancing work productivity in IBS may require treatments that improve both gastrointestinal (GI) and non-GI symptom intensity, while also modifying the cognitive and behavioral responses to bowel symptoms and the contexts in which they occur.

The utility of diagnostic criteria in irritable bowel syndrome (see Section 2.3)

IBS is defined by abdominal pain or discomfort that occurs in association with altered bowel habits over a period of at least three months. Individual symptoms have limited accuracy for diagnosing IBS and, therefore, the disorder should be considered as a symptom complex. Although no symptom-based diagnostic criteria have ideal accuracy for diagnosing IBS, traditional criteria, such as Kruis and Manning, perform at least as well as Rome I criteria; the accuracy of Rome II and Rome III criteria has not been evaluated.

IBS is a chronic illness of disordered bowel function and abdominal pain or discomfort that is distinguished by the absence of biochemical markers or structural abnormalities. As individual symptoms have imperfect accuracy in diagnosing IBS, criteria have been developed to identify a combination of symptoms to diagnose the condition. Manning *et al.* promulgated the original account of this approach. Two of four studies that have evaluated the accuracy of the Manning criteria suggested they perform well, with a sensitivity of 78% and specificity of 72%. Kruis *et al* developed another set of criteria; three of four studies that examined the accuracy of the Kruis symptom score suggested it provides an excellent positive predictive value with a high sensitivity (77%) and specificity (89%). The Rome criteria subsequently were developed and have undergone three iterations. One study has evaluated the accuracy of Rome I criteria, and determined it had a sensitivity of 71% and specificity of 85%; Rome II and Rome III have not yet been evaluated. None of the symptom-based diagnostic criteria have an ideal accuracy, and the Rome criteria, in particular, have been inadequately evaluated. The ACG Task Force believes that a practical definition, i.e., one that is simple to use and incorporates key features of previous diagnostic criteria would be clinically useful. Therefore, we have defined IBS as abdominal pain or discomfort that occurs in association with altered bowel habits over a period of at least 3 months.

The role of alarm features in the diagnosis of IBS (see Section 2.4)

Overall, the diagnostic accuracy of alarm features is disappointing. Rectal bleeding and nocturnal pain offer little discriminative value in separating patients with IBS from those with organic diseases. Whereas anemia and weight loss have poor sensitivity for organic diseases, they offer very good specificity. As such, in patients who fulfill symptom-based criteria of IBS, the absence of selected alarm features, including anemia, weight loss, and a family history of colorectal cancer, inflammatory bowel disease, or celiac sprue, should reassure the clinician that the diagnosis of IBS is correct.

Patients with typical IBS symptoms also may exhibit so-called "alarm features" that increase concern organic disease may be present. Alarm features include rectal bleeding, weight loss, iron deficiency anemia, nocturnal symptoms, and a family history of selected organic diseases including colorectal cancer, inflammatory bowel disease (IBD), and celiac sprue. Usually, it is recommended that patients who exhibit alarm features undergo further investigation, particularly with colonoscopy to rule out organic disease, e.g., colorectal cancer.

Based on a review of the literature, the accuracy of such alarm features is disappointing. Rectal bleeding and nocturnal pain offer little discriminative value in separating patients with IBS from those with organic diseases. Whereas anemia and weight loss have poor sensitivity for organic diseases, they offer very good specificity. As such, in patients who fulfill symptom-based criteria of IBS, the absence of selected alarm features, including anemia, weight loss, and a family history of colorectal cancer, IBD, or celiac sprue, should reassure the clinician that the diagnosis of IBS is correct.

The role of diagnostic testing in patients with IBS symptoms (see Section 2.5)

Routine diagnostic testing with complete blood count, serum chemistries, thyroid function studies, stool for ova and parasites, and abdominal imaging is not recommended in patients with typical IBS symptoms and no alarm features because of a low likelihood of uncovering organic disease (Grade 1C). Routine serologic screening for celiac sprue should be pursued in patients with IBS-D and IBS-M (Grade 1B). Lactose breath testing can be considered when lactose maldigestion remains a concern despite dietary modification (Grade 2B). Currently, there are insufficient data to recommend breath testing for small intestinal bacterial overgrowth in IBS patients (Grade 2C). Because of the low pretest probability of Crohn's disease, ulcerative colitis, and colonic neoplasia, routine colonic imaging is not recommended in patients younger than 50 years of age with typical IBS symptoms and no alarm features (Grade 1B). Colonoscopic imaging should be performed in IBS patients with alarm features to rule out organic diseases and in those over the age of 50 years for the purpose of colorectal cancer screening (Grade 1C). When colonoscopy is performed in patients with IBS-D, obtaining random biopsies should be considered to rule out microscopic colitis (Grade 2C).

As IBS is a disorder of heterogeneous pathophysiology for which specific biomarkers are not yet available, diagnostic tests are performed to exclude organic diseases that may masquerade as IBS and, in so doing, reassure both the clinician and the patient that the diagnosis of IBS is correct. Historically, IBD, colorectal cancer, diseases associated with malabsorption, systemic hormonal disturbances, and enteric infections are of the greatest concern to clinicians caring for patients with IBS symptoms. When deciding on the necessity of a diagnostic test in a patient with IBS symptoms, one should first consider the pretest probability of the disease in question. Based on currently available evidence, the Task Force feels that patients who fulfill the symptom-based diagnostic criteria for IBS and who have no alarm features require little formal testing before arriving at the diagnosis of IBS. The likelihood of uncovering important organic disease by a complete blood count, serum chemistries, and thyroid function studies is low and no greater in IBS patients than in healthy controls. Similarly, the yield of stool ova and parasite examination and abdominal ultrasound is low. For these reasons, the routine use of these tests in IBS patients without alarm features is not recommended. There is emerging evidence, however, to suggest that the prevalence of celiac sprue is higher among patients with IBS than in controls. Based on this evidence and decision analytic modeling data that suggest cost effectiveness, the Task Force recommends routine serologic screening for celiac sprue in patients with IBS-D or IBS-M. Evidence also suggests that the prevalence of lactose maldigestion is higher among IBS patients than in healthy controls. Furthermore, the clinical response to lactose maldigestion may be exaggerated in IBS patients compared with controls. For these reasons, the Task Force suggests that providers question patients about a link between lactose ingestion and their IBS symptoms. If, after a careful history and review of a food diary, questions remain regarding the presence of lactose maldigestion, performance of a lactose hydrogen breath test can be considered. A great deal of attention has been focused on the potential role of small intestinal bacterial overgrowth (SIBO) in the pathogenesis of IBS symptoms. The available data on this topic have yielded conflicting results. On a practical level, currently there is no available gold standard test to diagnose SIBO. For these reasons, the Task Force feels that there is insufficient evidence to recommend the performance of lactulose or glucose breath tests to identify SIBO in patients with IBS. Colonic imaging in an IBS patient with no alarm features is unlikely to reveal structural disease that might explain the patient's symptoms. Studies suggest that the prevalence of structural disease identified by colonic imaging is less than 1.3%. For this reason, the Task Force recommends that patients younger than 50 years of age who do not have alarm features need not undergo routine colonic imaging. Patients with IBS symptoms who have alarm features such as anemia or weight loss or those who are older than 50 years of age should undergo

colonic imaging to exclude organic disease. There is emerging evidence to suggest that microscopic colitis can masquerade as IBS-D, and therefore, when patients with IBS-D undergo colonoscopy, performance of random mucosal biopsies should be considered. In patients whose symptoms are consistent with IBS and who also have alarm features, the nature and severity of the symptoms as well as the patient's expectations and concerns influence the choice of diagnostic testing.

Diet and irritable bowel syndrome (see Section 2.6)

Patients often believe that certain foods exacerbate their IBS symptoms. There is, however, insufficient evidence that food allergy testing or exclusion diets are efficacious in IBS and their routine use outside of a clinical trial is not recommended (Grade 2C).

Approximately 60% of IBS patients believe that food exacerbates their symptoms, and research has suggested that allergy to certain foods could trigger IBS symptoms. A systematic review identified eight studies that assessed a symptomatic response to exclusion diets in 540 IBS subjects. Studies reported a positive response in 12.5–67% of patients, but the absence of control groups makes it is unclear whether these rates simply reflect a placebo response. There is no correlation between foods that patients identify as a cause of their IBS symptoms and the results of food allergy testing. One randomized trial suggested that patients with IBS can identify foods that cause symptoms, but two subsequent trials have not confirmed this.

Effectiveness of dietary fiber, bulking agents, and laxatives in the management of irritable bowel syndrome (see Section 2.7)

Psyllium hydrophilic mucilloid (ispaghula husk) is moderately effective and can be given a conditional recommendation (Grade 2C). A single study reported improvement with calcium polycarbophil. Wheat bran or corn bran is no more effective than placebo in the relief of global symptoms of IBS and cannot be recommended for routine use (Grade 2C). Polyethylene glycol (PEG) laxative was shown to improve stool frequency—but not abdominal pain—in one small sequential study in adolescents with IBS-C (Grade 2C).

Dietary fiber supplements studied in patients with IBS include wheat and corn bran. Bulking agents include psyllium hydrophilic mucilloid (ispaghula husk) and calcium polycarbophil. Most trials of these agents are suboptimal and had small sample sizes, short duration of follow-up, and were conducted before modern standards for study design were established.

Neither wheat bran nor corn bran reduced global IBS symptoms. Psyllium hydrophilic mucilloid improved global IBS symptoms in four of the six studies reviewed. Meta-analysis showed that the relative risk of IBS symptoms not improving with psyllium was 0.78 (95% CI = 0.63–0.96) and the number needed to treat (NNT) was six (95% CI = 3–50). A single study of calcium polycarbophil showed benefit. Adverse events in these studies were not reported systematically. Bloating may be a risk with these agents.

No placebo-controlled, randomized study of laxatives in IBS has been published. Laxatives have been studied mostly in patients with chronic constipation. A single small sequential study compared symptoms before and with PEG laxative treatment in adolescents with IBS-C. Stool frequency improved from an average of 2.07 ± 0.62 bowel movements per week to 5.04 ± 1.51 bowel movements per week ($P < 0.05$), but there was no effect on pain intensity.

Effectiveness of antispasmodic agents, Including peppermint oil, in the management of irritable bowel syndrome (see Section 2.8)

Certain antispasmodics (hyoscine, cimetropium, pinaverium, and peppermint oil) may provide short-term relief of abdominal pain/discomfort in IBS (Grade 2C). Evidence for long-term efficacy is not available. Evidence for safety and tolerability is limited (Grade 2C).

There is evidence for the efficacy of antispasmodics as a class and some peppermint oil preparations (which also may act as antispasmodics) in IBS. There are, however, significant variations in the availability of these agents in different countries; little of the data is recent; early trials vary considerably in terms of inclusion criteria, dosing schedule, duration of therapy, and study endpoints; and many are of poor quality and frequently fail to differentiate between the effects of these agents on global symptoms and individual symptoms, such as pain. Furthermore, the adverse event profile of these agents has not been defined adequately.

Effectiveness of antidiarrheals in the management of irritable bowel syndrome (see Section 2.9)

The antidiarrheal agent loperamide is not more effective than placebo at reducing pain, bloating, or global symptoms of IBS, but it is an effective agent for the treatment of diarrhea, reducing stool frequency, and improving stool consistency (Grade 2C). Randomized controlled trials comparing loperamide with other antidiarrheal agents have not been performed. Safety and tolerability data on loperamide are lacking.

Patients with IBS-D display faster intestinal transit compared with healthy subjects and, therefore, agents that delay intestinal transit may be beneficial in reducing symptoms. Loperamide is the only antidiarrheal agent sufficiently evaluated in randomized controlled trials (RCTs) for the treatment of IBS-D. Of the two RCTs evaluating the effectiveness of loperamide in the treatment of IBS with diarrhea-predominant symptoms, there were no significant effects in favor of loperamide compared with placebo. The trials were both double-blinded, but the proportion of women in each trial was unclear and neither reported adequate methods of randomization or adequate concealment of allocation. Each trial used a clinical diagnosis of IBS supplemented by negative investigations to define the condition. Loperamide had no effect on symptoms of bloating, abdominal discomfort or global IBS symptoms. There was a beneficial

effect to improve stool frequency and consistency, although the overall impact of loperamide on IBS symptoms was not statistically significant. Both trials reported that all subjects in the loperamide group had improved stool consistency compared with controls. Based on these results, loperamide is considered an effective therapy for diarrhea. Inadequate data on adverse events was reported.

Effectiveness of antibiotics in the management of irritable bowel syndrome (see Section 2.10)

A short-term course of a nonabsorbable antibiotic is more effective than placebo for global improvement of IBS and for bloating (Grade IB). There are no data available to support the long-term safety and effectiveness of nonabsorbable antibiotics for the management of IBS symptoms.

Rifaximin, a nonabsorbable antibiotic, has demonstrated efficacy in three RCTs evaluating 545 patients with IBS. All of these RCTs demonstrated statistically significant improvement in global IBS symptoms, bloating symptoms, or both in rifaximin-treated patients compared with placebo-treated patients. Moreover, these three RCTs were well designed, meeting all criteria for appropriately designed RCTs (i.e., truly randomized studies with concealment of treatment allocation, implementation of masking, completeness of follow-up, and intention-to-treat analysis) and meeting most criteria of the Rome committee for design of treatment trials of functional GI disorders. Rifaximin is not Food and Drug Administration (FDA)-approved for treatment of IBS, although it is FDA-approved for treatment of traveler's diarrhea at a dose of 200 mg twice daily for three days; IBS trials used higher doses of rifaximin for longer periods: 400 mg three times daily for 10 days, 400 mg twice daily for 10 days, and 550 mg twice daily for 14 days. Also, the largest RCT ($n = 388$ patients) only examined patients with IBS-D. Rifaximin-treated patients were 8–23% more likely to experience global improvement in their IBS symptoms, bloating symptoms, or in both, compared with placebo-treated patients. Rifaximin-treated patients also demonstrated significant improvement in diarrhea compared with placebo-treated patients. Based on these results, rifaximin is most likely to be efficacious in IBS-D patients or IBS patients with a predominant symptom of bloating; the appropriate dosage is approximately 1,100–1,200 mg/day for 10–14 days. Minimal safety data were reported in these trials, but rifaximin-treated patients reportedly tolerated antibiotics without severe adverse events. However, given the often chronic and recurrent nature of IBS symptoms and the theoretical risks related to long-term treatment with any antibiotic, a recommendation regarding continuous or intermittent use of this agent in IBS must await further, long-term studies. It must also be stressed that available data on rifaximin is based on phase II studies; phase III studies have yet to be reported.

Neomycin, metronidazole, and clarithromycin also have been evaluated for the management of IBS. In a single RCT of 111 patients, neomycin-treated patients were more likely to experience 50% improvement in global IBS symptoms compared with placebo-treated patients (43 vs. 23%, $p < 0.05$). In a single RCT, clarithromycin was not significantly better than placebo. In one report, metronidazole-treated patients demonstrated significant improvement over placebo-treated patients, but data from this study were not presented in an extractable form. Overall adverse event data were not available for these trials, but no severe adverse events were reported.

Effectiveness of probiotics in the management of irritable bowel syndrome (see Section 2.11)

In single organism studies, lactobacilli do not appear effective for patients with IBS; bifidobacteria and certain combinations of probiotics demonstrate some efficacy (Grade 2C).

Probiotics possess a number of properties that may prove of benefit to patients with IBS. Interpretation of the available literature on the use of probiotics in IBS, however, is hampered by difficulties in comparing studies using probiotics that varied widely in terms of species, strains, preparations, and doses. Furthermore, and reflecting limitations in study design, the data are conflicting: the dichotomous data suggest that all probiotic therapies have a trend for being efficacious in IBS, whereas the continuous data indicate that *Lactobacilli* have no impact on symptoms; probiotic combinations improve symptoms; and there is a trend for *Bifidobacteria* to improve IBS symptoms. Another deficiency in study design is that most studies were of short-term, so we lack information on long-term use. Available safety data indicate that these preparations are well tolerated and free from serious adverse side effects in this population.

Effectiveness of the $5HT_3$ receptor antagonists in the management of irritable bowel syndrome (see Section 2.12)

The 5-HT_3 receptor antagonist alosetron is more effective than placebo at relieving global IBS symptoms in male (Grade 2B) and female (Grade 2A) IBS patients with diarrhea. Potentially serious side effects including constipation and colon ischemia occur more commonly in patients treated with alosetron compared with placebo (Grade 2A). The benefits and harms balance for alosetron is most favorable in women with severe IBS and diarrhea who have not responded to conventional therapies (Grade 1B). The quality of evidence for efficacy of 5-HT_3 antagonists in IBS is high.

Alosetron remains the only 5-HT_3 receptor antagonist approved for the treatment of women with severe IBS-D in the United States. In eight large, well-designed clinical trials that evaluated alosetron use in 4,840 patients, this drug has demonstrated superiority over placebo for abdominal pain, urgency, global IBS symptoms, and diarrhea-related complaints. Considering the primary therapeutic endpoint as "adequate relief" of abdominal pain and discomfort or urgency, the relative risk of IBS persisting with alosetron treatment was 0.79 (95% CI = 0.69-0.91 with NNT = 8; 95% CI = 5–17). In one placebo-controlled study, alosetron demonstrated sustained relief of abdominal pain and discomfort as well as urgency in

IBS-D patients for up to 48 weeks, with a safety profile comparable to that of placebo. Another recent randomized, placebo-controlled trial found alosetron to be more effective for abdominal pain and discomfort than placebo in men with IBS-D (53 vs. 40%, $P < 0.001$).

In a recent systematic review which included data from seven studies, patients randomized to alosetron were statistically significantly more likely to report an adverse event than those randomized to placebo (relative risk (RR) of adverse event = 1.18; 95% CI = 1.08–1.29). The number needed to harm (NNH) with alosetron was 10 (95% CI = 7–16). Dose-dependent constipation was the most commonly reported adverse event with alosetron (1 mg twice daily = 29%; 0.5 mg twice daily = 11%). Another systematic review of the clinical and postmarketing surveillance data from IBS patients and the general population confirmed a greater incidence of severe complicated constipation and ischemic colitis in patients taking alosetron, however, the incidence of these events was low, with a rate of 1.1 cases of ischemic colitis and 0.66 cases of complicated constipation per 1,000 patients-years of alosetron use.

Current use of alosetron is regulated by a prescribing program set forth by the FDA and administered by the manufacturer (Prometheus Laboratories, San Diego, CA). The recommended starting dose of alosetron is 0.5 mg twice daily. If after four weeks, the drug is well tolerated but the patient's IBS-D symptoms are not adequately controlled, the dose can be escalated to 1 mg twice daily. Alosetron should be discontinued if the patient develops symptoms or signs suggestive of severe constipation or ischemic colitis or if there is no clinical response to the 1 mg twice daily dose after four weeks.

Effectiveness of $5HT_4$ (serotonin) receptor agonists in the management of irritable bowel syndrome (see Section 2.13)

The 5-HT_4 receptor agonist tegaserod is more effective than placebo at relieving global IBS symptoms in female IBS-C patients (Grade 1A) and IBS-M patients (Grade 1B). The most common side effect of tegaserod is diarrhea (Grade 1A). A small number (0.11%) of cardiovascular events (myocardial infarction, unstable angina, or stroke) were reported among patients who had received tegaserod in clinical trials.

Currently, there are no 5-HT_4 receptor agonists available for use in North America. Tegaserod (6 mg twice daily) has been approved by the FDA for the treatment of IBS with constipation in women. Tegaserod was evaluated in multiple RCTs that were very well designed, meeting all criteria for appropriately designed RCTs (i.e., truly randomized studies with concealment of treatment allocation, implementation of masking, completeness of follow-up and intention-to-treat analysis) and meeting almost all criteria of the Rome committee for design of treatment trials of functional GI disorders. Each of the RCTs assessing the efficacy of tegaserod 6 mg twice daily demonstrated that it was superior to placebo for global IBS symptom improvement. Based on the defined end point of global IBS symptom improvement, tegaserod-treated patients were 5–19% more likely to experience satisfactory improvement of global IBS symptoms than were placebo-treated patients. Tegaserod is also the only 5-HT_4 agonist that has been evaluated in an IBS-M population. In a well-designed RCT, tegasarod-treated patients with the IBS-M were 15% more likely to demonstrate improvement in global IBS symptoms compared with placebo-treated patients. In most RCTs, tegaserod-treated patients were significantly more likely to experience improvement in abdominal discomfort, satisfaction with bowel habits, and bloating than placebo-treated patients. Diarrhea occurred significantly more often in tegaserod-treated patients compared with placebo-treated patients, most trials reporting diarrhea in approximately 10% of tegaserod-treated patients and in approximately 5% of placebo-treated patients. Approximately 1–2% of tegaserod-treated patients discontinued tegaserod because of diarrhea.

Tegaserod was removed from the market in March of 2007 after examination of the total clinical trial database revealed that cardiovascular events were more frequent in tegaserod-treated patients ($n = 11{,}614$) compared with placebo-treated patients ($n = 7{,}031$; 0.11% vs. 0.01%). Thirteen tegaserod-treated patients had cardiovascular events including myocardial infarction ($n = 4$), unstable angina ($n = 6$), and cerebral vascular accident ($n = 3$) whereas one placebo-treated patient had a transient ischemic attack. Currently, tegaserod is not available under any treatment investigational new drug protocol, but it is available from the FDA through an emergency investigational new drug protocol.

Renzapride and cisapride did not produce any statistically significant improvement in global IBS symptoms compared with placebo.

Effectiveness of the selective C-2 chloride channel activators in the management of irritable bowel syndrome (see Section 2.14)

Lubiprostone in a dose of 8 μg twice daily is more effective than placebo in relieving global IBS symptoms in women with IBS-C (Grade 1B).

Lubiprostone (8 μg twice daily) is approved by the FDA for the treatment of IBS-C in women on the basis of two well-designed, large clinical trials. Based on a conservative endpoint designed to minimize placebo response, lubiprostone improved global IBS-C symptoms in nearly twice as many subjects as did placebo (18 vs. 10%, $P < 0.001$). Lubiprostone also improved individual symptoms of IBS including abdominal discomfort/pain, stool constancy, straining, and constipation severity. No one symptom appeared to drive the global improvement. Effects were well maintained for up to 48 weeks in open-label continuation studies. Side effects included nausea (8%), diarrhea (6%) and abdominal pain (5%), but were less frequent in these IBS-C studies than in previous studies of patients with chronic constipation in which a larger dose (24 μg twice daily) of lubiprostone was used. Lubiprostone should not be used in patients with mechanical bowel obstruction or preexisting diarrhea. Women capable of bearing children should have a documented negative pregnancy test before starting therapy and should be advised to

use contraception while taking lubiprostone. Studies need to be conducted in men before this agent can be recommended for use in men.

Effectiveness of antidepressant agents in the management of irritable bowel syndrome (see Section 2.15)

Tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs) are more effective than placebo at relieving global IBS symptoms, and appear to reduce abdominal pain. There are limited data on the safety and tolerability of these agents in patients with IBS (Grade 1B).

Nine trials were identified that tested TCAs in various doses for IBS. TCAs clearly were superior to placebo (NNT = 4, 95% CI = 3–6). There is no convincing evidence that the dose needed has to be in the antidepressant range, and most trials tested low-dose TCAs. In two of the trials, abdominal pain was the primary endpoint and a significant benefit was observed.

Five trials that assessed SSRIs also showed a benefit in IBS over placebo (NNT = 3.5). Theoretically, SSRIs should be of most benefit for IBS-C, whereas TCAs should be of greatest benefit for IBS-D because of their differential effects on intestinal transit time, but there is a lack of available data from the clinical trials to assess this clinical impression.

The safety of using antidepressants in IBS remains poorly documented, although data suggest that the SSRIs are tolerated better than the TCAs. No data on the efficacy of SSRIs or other new antidepressant drug classes are available in this literature.

Effectiveness of psychological therapies in the management of irritable bowel syndrome (see Section 2.16)

Psychological therapies, including cognitive therapy, dynamic psychotherapy, and hypnotherapy, but not relaxation therapy, are more effective than usual care in relieving global symptoms of IBS (Grade 1B).

Among patients with IBS who seek care, particularly in subspecialty practice, the majority have anxiety, depression, or features of somatization. The overlap of psychologic disorders with IBS has led to studies evaluating the benefits of psychological therapies in reducing IBS symptoms. Psychological therapies include cognitive behavioral therapy, dynamic psychotherapy, hypnotherapy, and relaxation therapy.

In 20 RCTs that compared various psychological therapies with usual care, there was a benefit for cognitive behavioral therapy, dynamic psychotherapy, and hypnotherapy, but not relaxation therapy. There have been more studies of cognitive behavioral therapy than any other management approaches, and a high-quality, large North American trial of 12-week duration clearly showed its benefit. Psychological therapies are not documented to have any serious adverse events, although the mechanisms of their benefit remain unclear.

Effectiveness of herbal therapies and acupuncture in the management of irritable bowel syndrome (see Section 2.17)

Available RCTs mostly tested unique Chinese herbal mixtures, and appeared to show a benefit. It is not possible to combine these studies into a meaningful meta-analysis, however, and overall, any benefit of Chinese herbal therapy in IBS continues to potentially be confounded by the variable components used and their purity. Also, there are significant concerns about toxicity, especially liver failure, with use of any Chinese herbal mixture. A systematic review of trials of acupuncture was inconclusive because of heterogeneous outcomes. Further work is needed before any recommendations on acupuncture or herbal therapy can be made.

Emerging therapies for irritable bowel syndrome (see Section 2.18)

Our expanding knowledge of the pathogenesis of IBS has led to the identification of a wide variety of novel therapeutic agents. Broadly speaking, there are agents in development for IBS with predominantly peripheral effects and some with both peripheral and central effects. Examples of classes of drugs with predominantly peripheral effects include agents that affect chloride secretion, calcium channel blockers, opioid receptor ligands, and motilin receptor ligands. Drug classes, which exert effects both peripherally and centrally, include novel serotonergic agents, corticotropin-releasing hormone antagonists, and autonomic modulators.

An Evidence-Based Systematic Review on the Management of Irritable Bowel Syndrome

American College of Gastroenterology IBS Task Force:
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Section 2.1 Methodology for systematic reviews of irritable bowel syndrome therapy, levels of evidence, and grading of recommendations

We have conducted a series of systematic reviews on the diagnostic criteria, the value of diagnostic tests, and the efficacy of therapy in IBS. We also performed a narrative review of the epidemiology of IBS. There have been several systematic reviews of therapy for IBS (1–5), but these either have not quantitatively combined the data into meta-analyses (1–3) or have inaccuracies in applying eligibility criteria and data extraction (4,5). We have, therefore, repeated all systematic reviews of IBS and synthesized the data where appropriate.

Systematic review methodology

For all reviews, we evaluated manuscripts that studied adults using any definition of IBS. This included a clinician-defined diagnosis, Manning criteria (6), the Kruis score (7), or Rome I (8), II (9), or III (10) criteria.

For reviews of diagnostic tests, we included case series and case-control studies that evaluated serologic tests for celiac sprue (anti-gliadin, anti-endomysial, and tissue transglutaminase antibodies), lactose hydrogen breath tests, and tests for small bowel bacterial overgrowth (lactulose and glucose hydrogen breath test or jejunal aspirates).

For reviews of therapies of IBS, we included only parallel group RCTs comparing active intervention with either placebo or no therapy.

The following treatments were considered:

(i) Diet
(ii) Fiber, bulking agents, and laxatives
(iii) Antispasmodics and Peppermint Oil
(iv) Antidiarrheal agents
(v) Antibiotic therapy
(vi) Probiotic therapy
(vii) 5HT3 antagonists
(viii) 5HT4 agonists
(ix) Selective C-2 chloride channel activators (Lubiprostone)
(x) Antidepressants
(xi) Psychological therapies
(xii) Herbal therapies and acupuncture
(xiii) Emerging therapies

Subjects needed to be followed up for at least one week. The trial needed to include one or more of the following outcome measures:

(i) Global assessment of IBS cure or improvement
(ii) Abdominal pain cure or improvement
(iii) Global IBS symptom or abdominal pain scores

Search strategy for identification of studies

Medline (1966–June 2008), Embase (1988–June 2008), and the Cochrane Controlled Trials Register (Issue 2, 2008) electronic databases were searched. An example of the Medline search is given below.

IBS patients were identified with the terms *irritable bowel syndrome* and *functional diseases*, *colon* (both as medical subject heading (MeSH) and free text terms), and *IBS*, *spastic colon*, *irritable colon*, and *functional* adj5 (adj5 is a term used by Medline for words that appear within 5 adjectives of each other) *bowel* (as free text terms).

Studies identified from this search were combined with the following terms used to identify therapies for IBS: *dietary fiber*, *cereals*, *psyllium*, *sterculia*, *karaya gum*, *parasympatholytics*, *scopolamine*, *trimebutine*, *muscarinic antagonists*, and the following free text terms: *bulking agent*, *psyllium fiber*, *fiber*, *husk*, *bran*, *ispaghula*, *wheat bran*, *spasmolytics*, *spasmolytic agents*, *antispasmodics*, *mebeverine*, *alverine*, *pinaverium bromide*, *otilonium bromide*, *cimetropium bromide*, *hyoscine butyl bromide*, *butylscopolamine*, *peppermint oil*, *loperamide and colpermin*, *serotonin antagonists*, *serotonin agonists*, *cisapride*, *receptors* (*serotonin*, *5-HT$_3$*), *and receptors* (*serotonin*, *5-HT$_4$*; both as MeSH terms and free text terms), and the following free text terms: *5-HT$_3$*, *5-HT$_4$*, *alosetron*, *cilansetron*, *tegaserod*, *and renzapride*, *psychotropic drugs*, *antidepressive agents*, *antidepressive agents (tricyclic)*, *desipramine*, *imipramine*, *trimipramine*, *doxepin*, *dothiepin*, *nortriptyline*, *amitriptyline*,

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selective serotonin re-uptake inhibitors, *paroxetine*, *sertraline*, *fluoxetine*, *citalopram*, *venlafaxine*, *cognitive therapy*, *psychotherapy*, *behaviour therapy*, *relaxation techniques*, *and hypnosis* (both as MeSH terms and free text terms), and the following free text terms: *behavioral therapy*, *relaxation therapy*, *and hypnotherapy. Saccharomyces*, *Lactobacillus*, *Bifidobacterium*, *Escherichia coli* or probiotics (MeSH and free text terms).
An RCT filter was applied to the electronic searches. The searches were limited to humans. A recursive search of the bibliography of relevant articles also was conducted.

DDW abstract books were hand searched between 2000 and 2008; UEGW abstract books were hand searched between 2000 and 2007. Authors of trial reports that did not give enough detail for adequate data extraction were contacted and asked to contribute full datasets. Experts in the field were contacted for leads on unpublished studies and no language restrictions were applied.

Trials were assessed for risk of bias according to three characteristics: method of randomization, method of concealment of treatment allocation, and implementation of masking. In addition the quality of studies were graded according to the Jadad scale (11) with a score of ≥4 being considered a high quality.

Eligibility, quality, and outcome data were extracted by the lead reviewer (Paul Moayyedi) and by a masked second reviewer (Alex Ford) on specially developed forms. Any discrepancy was resolved by consensus using a third reviewer (Nicholas Talley).

Data were extracted as intention-to-treat analyses, and dropouts were assumed to be treatment failures.

Data synthesis
Whenever possible, any improvement of global IBS symptoms as a binary outcome was taken as the primary outcome measure. If this was not available, improvement in abdominal pain was used. The impact of interventions was expressed as RR of IBS symptoms not improving together with 95% confidence intervals. If there were sufficient data, relative risks were combined using the DerSimonian and Laird random effects model (12). Tests of heterogeneity also were reported (13). When the test of heterogeneity was significant ($p<0.10$ and/or $I^2>25\%$), the reasons for this were explored by evaluating differences in study population, study design, or study endpoints in subgroup analyses. Publication bias or other causes of small study effects were evaluated using tests for funnel plot asymmetry (14).

The NNT was calculated as the inverse of the risk difference from the meta-analysis and checked using the formula:

$$NNT = \frac{100}{RRR \times BR}$$

(RRR = relative risk reduction, BR = baseline risk).

Methodology for assessing levels of evidence and grading recommendations
A commonly used system for grading recommendations in evidence-based guidelines (15) was employed to assess the quality of evidence and the strength of recommendation. This system, which is outlined in **Table 1**, includes the assessment of quality of evidence and benefit-risk profile in the graded recommendation. The grading scheme classifies recommendations as strong (Grade 1) or weak (Grade 2) according to the balance of benefits, risks, burdens, and sometimes costs, based on evaluation by experts. Also, this system classifies the quality of evidence as high (Grade A), moderate (Grade B), or low (Grade C) according to the quality of study design, the consistency of results among individual studies, and directness and applicability of study endpoints. With this graded recommendation, the clinician receives guidance about whether or not recommendations should be applied to most patients and whether or not recommendations are likely to change in the future after production of new evidence. Grade 1A recommendations represent a "strong recommendation that can apply to most patients in most circumstances and *further evidence is unlikely to change our confidence in the estimate of treatment effect.*" In the opinion of the Task Force, a Grade 1A recommendation can only be justified by data from thousands of patients. Currently-available IBS therapies have not been studied in thousands of appropriate patients. Therefore, no currently available IBS therapy has received a Grade 1A recommendation. The system is most appropriate for IBS management strategies and is less relevant for definitions and epidemiologic data, so statements in the epidemiologic section are not graded.

Section 2.2 The burden of illness of irritable bowel syndrome

IBS is a prevalent and expensive condition that is associated with a significantly impaired HRQOL and reduced work productivity. Based on strict criteria, 7–10% of people have IBS worldwide. Community-based data indicate that IBS-D and IBS-M subtypes are more prevalent than IBS-C, and that switching among subtype groups may occur. IBS is 1.5 times more common in women than in men, is more common in lower socioeconomic groups, and is more commonly diagnosed in patients younger than 50 years of age. Patients with IBS visit the doctor more frequently, use more diagnostic tests, consume more medications, miss more workdays, have lower work productivity, are hospitalized more frequently, and consume more overall direct costs than patients without IBS. Resource utilization is highest in patients with severe symptoms, and poor HRQOL. Treatment decisions should be tailored to the severity of each patient's symptoms and HRQOL decrement.

IBS is a prevalent condition that can affect patients physically, psychologically, socially, and economically. Awareness of and knowledge about this burden of illness serves several purposes. For patients, it emphasizes that many others have IBS, and that people suffering from IBS should not feel alone with their diagnosis or disease-related experiences. For healthcare providers, it highlights that IBS is a large part of both internal medicine and gastroenterology practices. Moreover, it allows providers to improve their understanding of the impact of IBS on their

Table 1. Grading recommendations

Grade of Recommendation/description	Benefit vs. risk and burdens	Methodological quality of supporting evidence	Implications
1A. Strong recommendation, high-quality evidence	Benefits clearly outweigh risk and burdens, or vice versa	RCTs without important limitations or overwhelming evidence from observational studies	Strong recommendation, can apply to most patients in most circumstances. Further evidence is unlikely to change our confidence in the estimate of effect
1B. Strong recommendation, moderate-quality evidence	Benefits clearly outweigh risk and burdens, or vice versa	RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies	Strong recommendation, can apply to most patients in most circumstances. Higher quality evidence may well change our confidence in the estimate of effect
1C. Strong recommendation, low-quality or very low-quality evidence	Benefits clearly outweigh risk and burdens, or vice versa	Observational studies or case series	Strong recommendation can apply to most patients in most circumstances. Higher quality evidence is very likely to change our confidence in the estimate of effect
2A. Weak recommendation, high-quality evidence	Benefits closely balanced with risks and burden	RCTs without important limitations or overwhelming evidence from observational studies	Weak recommendation, best action may differ depending on circumstances or patients' or societal values. Further evidence is unlikely to change our confidence in the estimate of effect
2B. Weak recommendation, moderate-quality evidence	Benefits closely balanced with risks and burden	RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies	Weak recommendation, best action may differ depending on circumstances or patients' or societal values. Higher quality evidence may well change evidence our confidence in the estimate of effect
2C. Weak recommendation, low-quality or very low-quality evidence	Uncertainty in the estimates of benefits, risks, and burden; benefits, risk, and burden may be closely balanced	Observational studies or case series	Very weak recommendations; other alternatives may be equally reasonable. Higher quality evidence is likely to change our confidence in the estimate of effect

RCT, randomized controlled trial.

patients' well being, and then act on this insight by selecting treatments tailored to each patient's symptoms and HRQOL decrement. For research funding and drug-approval authorities, it shows that IBS is far more than a mere nuisance, and is instead a condition with a prevalence and HRQOL impact that matches other major diagnoses such as diabetes, hypertension, or kidney disease (16,17). For employers and healthcare insurers, it reveals the overwhelming direct and indirect expenditures related to IBS, and provides a business rationale to ensure that IBS is treated effectively. The objective of this section is to review key data regarding the burden of illness of IBS, including: (1) the prevalence of IBS and its subtypes; (2) the age of onset and gender distribution of IBS; (3) the effect of IBS on HRQOL; and (4) the economic burden of IBS, including direct and indirect expenditures and their clinical predictors.

Previous systematic reviews have measured the prevalence of IBS in both North American and European nations (18,19). Prevalence estimates range from 1% to over 20%. This wide range indicates that IBS prevalence, like prevalence of all diseases, depends on several variables, including the case-finding definition employed (e.g., Manning criteria vs. Rome criteria), the characteristics of the source population (e.g., primary vs. secondary care), and the methodology and sampling frame of the studies. To refine the prevalence estimate, we performed an updated systematic review to target studies that only used Rome definitions, drew upon patients from the general adult community (i.e., not exclusively from primary or secondary care), and included patients who were not selected specifically (e.g., not evaluating IBS in subjects with reflux symptoms or in twins). We identified four eligible studies evaluating 32,638 North American subjects and found that IBS prevalence varied between 5 and 10% with a pooled prevalence of 7% (95% CI = 6–8%) (20–23). Although previous reviews indicated that IBS patients are divided evenly among the three major subgroups (IBS-D, IBS-C, and IBS-M) (24), the true prevalence of IBS subtypes in North America remains unclear; one study suggested that IBS with diarrhea is the most common subtype (21), whereas another indicated that mixed-type IBS is most common (22).

There are several demographic predictors of IBS, including gender, age, and socioeconomic status. The odds of having IBS are higher in women than in men (pooled OR = 1.46; 95% CI = 1.13–1.88) (20–23), although IBS is not simply a disorder of women. In fact, IBS is now recognized to be a key component of the Gulf War Syndrome, a multi-symptom complex affecting soldiers (a predominantly male population) deployed in the

1991 Gulf War (25–27). IBS is diagnosed more commonly in patients under the age of 50 years than it is in patients older than 50 years, although 2–6% of the latter group also suffer from the disorder (20–22). These data suggest that the pretest likelihood for IBS is higher in younger patients, but that patients of all ages may be diagnosed with IBS. Our review identified two studies that reported IBS prevalence by income strata (21,23), both of which revealed a graded decrease in IBS prevalence with increasing income: 8–16% of people earning less than $20,000 annually carry the diagnosis, compared with only 3–5% of people earning more than $75,000 (21,23).

Several studies have compared HRQOL in IBS patients and in healthy controls or controls with non-IBS medical disorders; these have been summarized in a previous systematic review (16). Data consistently demonstrate that patients with IBS score lower on all eight scales of the SF-36 HRQOL questionnaire compared with "normal" non-IBS cohorts. Patients with IBS have the same physical HRQOL as patients with diabetes, and a lower physical HRQOL compared with patients who have depression or gastroesophageal reflux disease (16,17). Perhaps more surprisingly, mental HRQOL scores on the SF-36 were lower in patients with IBS than in those with chronic renal failure—an organic condition marked by considerable physical and mental disability. This HRQOL decrement can, in some cases, be so severe as to raise the risk of suicidal behavior (28,29). The relationship between IBS and suicidality is independent of comorbid psychiatric diseases such as depression (28,29). Many of these studies, however, were performed in tertiary-care referral populations, and the HRQOL decrement and suicidality risk documented in these cohorts may not be applicable to community-based populations. It is possible that patients with IBS develop HRQOL decrements due to their disease, and also possible that some patients with diminished HRQOL subsequently develop IBS (30). Although the precise directionality of this relationship may vary from patient to patient, it is clear that IBS is strongly related to low HRQOL, and vice versa. Nonetheless, IBS is also likely to cause a negative impact on HRQOL, and failing to recognize this impact could undermine the physician–patient relationship and lead to dissatisfaction with care. Because HRQOL decrements are common in IBS, we recommend that clinicians perform routine screening for diminished HRQOL in their IBS patients. Treatment should be initiated when the symptoms of IBS are found to reduce functional status and diminish overall HRQOL. Furthermore, clinicians should remain wary of potential suicidal behavior in patients with severe IBS symptoms, and should initiate timely interventions if suicide forerunners are identified.

A practical limitation of determining HRQOL in busy outpatient settings is that its accurate measurement requires a thorough and often time-consuming evaluation of biologic, psychologic, and social health domains. To help providers gain better insight into their patients' HRQOL, a concise list of factors known to predict HRQOL in IBS might be helpful, which providers could then use to question patients routinely. Indeed, several studies have identified predictors of HRQOL in IBS (31–35), the most consistent of which is the severity of the predominant bowel symptom. Data from several studies indicate that in patients with IBS, HRQOL decreases in parallel with increasing symptom severity (29,31,33). It is therefore important not only to identify the predominant symptom of patients with IBS, but also to gauge its severity. Additional data indicate that physical HRQOL in IBS is related to the duration of symptom flares (≥24 h vs. <24 h) and the presence of abdominal pain (as opposed to "discomfort") and that mental HRQOL is associated with abnormalities in sexuality, mood, and anxiety (35). Perhaps more importantly, both domains share a common association with symptoms of chronic stress and vital exhaustion, including tiring easily, feeling low in energy, and experiencing sleep difficulties (35). Patients acknowledge that these symptoms adversely influence their ability to function by prompting avoidance of socially vulnerable situations (e.g., being away from restrooms) and activities (e.g., eating out for dinner). In contrast, HRQOL is not strongly determined by the presence of specific gastrointestinal symptoms (e.g., diarrhea, constipation, bloating, dyspepsia), extent of previous gastrointestinal evaluation (e.g., previous flexible sigmoidoscopy or colonoscopy), or common demographic characteristics (e.g., gender, age, marital status) (33).

The above findings suggest that rather than focusing on physiologic epiphenomena to gauge HRQOL (e.g., stool frequency, stool characteristics, subtype of IBS), it may be more efficient to assess HRQOL by gauging global symptom severity, addressing symptom-related fears and concerns, and identifying and eliminating factors contributing to vital exhaustion in IBS. In short, treating bowel symptoms in IBS is necessary, but may not be sufficient, to influence overall HRQOL. In addition to treating symptoms, providers should attempt to modify positively the cognitive interpretation of IBS symptoms—i.e., acknowledge and address the emotional context in which symptoms occur (36–38).

Patients with IBS consume a disproportionate amount of resources. Burden of illness studies estimate that there are 3.6 million physician visits for IBS in the United States annually, and that IBS care consumes over $20 billion in both direct and indirect expenditures (39). Moreover, patients with IBS consume over 50% more health care resources than matched controls without IBS (40,41). These data suggest that the economic burden of IBS stems not only from the high prevalence of the disease, but also from the disproportionate use of resources it causes.

It is unclear why patients with IBS consume a disproportionate amount of resources, especially in the light of data that diagnostic tests and procedures in IBS rarely detect alternative underlying conditions (see Section 2.5). Despite the dissemination and use of guidelines reinforcing these data (24), much of the cost of care in IBS arises from sequential diagnostic tests, invasive procedures, and abdominal operations (39,42). For example, patients with IBS are three times more likely than matched controls to undergo cholecystectomy (42) despite knowledge that IBS symptoms almost invariably persist following the surgery.

Similarly, nearly 25% of colonoscopies performed in patients younger than 50 years of age are for IBS symptoms (43), regardless of data that indicate colonoscopy has a low diagnostic yield in IBS, and that "negative" examinations fail to improve intestinal symptoms, do not augment HRQOL, and are unlikely to provide additional reassurance when compared with not performing colonoscopy (44). Resource utilization in IBS also is driven partly by the presence of comorbid somatization—a trait found in up to one-third of IBS patients that is characterized by the propensity to overinterpret normal physiologic processes (45,46). Patients with somatization typically report a barrage of seemingly unrelated physical complaints (e.g., back pain, tingling, headaches, temporomandibular joint pain, muscle aches) that may, in fact, be linked to underlying psychosocial distress (45,46). These patients are sometimes misclassified as having several underlying organic conditions, and subsequently undergo sequential diagnostic tests in chase of the disparate symptoms (47). There is a linear and highly significant relationship between levels of somatization and the amount of diagnostic testing in IBS, suggesting that providers should remain alert for somatization in IBS, and aggressively treat or refer somatization patients to an experienced specialist rather than performing potentially unnecessary diagnostic tests (47).

In addition to direct costs of care, IBS patients engender significant indirect costs of care as a consequence of both missing work and suffering impaired work performance while on the job. Employees with IBS are absent 3–5% of the workweek, and report impaired productivity 26–31% of the week (48–50)—rates that exceed those of non-IBS control employees by 20% (49); this is equivalent to 14 hours of lost productivity per 40-hour workweek. Compared with IBS patients who exhibit normal work productivity, patients with impaired productivity have more extraintestinal comorbidities (e.g., chronic fatigue syndrome, fibromyalgia, interstitial cystitis), and more disease-specific fears and concerns (50). In contrast, the specific profile of individual bowel symptoms does not undermine work productivity (50), suggesting that enhancing work productivity in patients with IBS may require treatments that improve both GI and non-GI symptom intensity, while also modifying the cognitive and behavioral responses to bowel symptoms and the contexts in which they occur. In other words, it may be inadequate to treat bowel symptoms alone without simultaneously addressing the emotional context in which the symptoms occur.

Section 2.3 The utility of diagnostic criteria in IBS

IBS is defined by abdominal pain or discomfort that occurs in association with altered bowel habits over a period of at least three months. Individual symptoms have limited accuracy for diagnosing IBS and, therefore, the disorder should be considered as a symptom complex. Although no symptom-based diagnostic criteria have ideal accuracy for diagnosing IBS, traditional criteria, such as Kruis and Manning, perform at least as well as Rome I criteria; the accuracy of Rome II and Rome III criteria has not been evaluated.

The ACG Task Force conducted a systematic review of the accuracy of symptom-based criteria in the diagnosis of IBS (51). Overall, eight studies (52–59) were identified involving 2,280 patients. In all studies, IBS was defined as a clinical diagnosis after investigations that included either a colonoscopy or a barium enema. The accuracy of individual symptoms was described in six studies (52–57) evaluating 1,077 patients. Symptoms such as abdominal pain, loose or frequent stools associated with pain, incomplete evacuation, mucus per rectum, and abdominal distention all had limited accuracy in diagnosing IBS. Lower abdominal pain had the highest sensitivity (90%) but very poor specificity (32%), whereas patient-reported visible abdominal distention had the highest specificity (77%) but low sensitivity (39%). A variety of criteria therefore have been developed to identify a combination of symptoms to diagnose IBS (see **Table 2**).

The first description of this approach was by Manning *et al.* (52) and there have been four studies evaluating the accuracy of Manning's criteria in 574 patients. Two studies (52,58) suggested these criteria performed well, whereas accuracy was poor in the other two studies (56,57). Overall, Manning's criteria had a pooled sensitivity of 78% and pooled specificity of 72% (51). The next description of symptom criteria was by Kruis *et al.*, and four studies (53–55) have described the accuracy of this approach in 1,166 patients. Three studies (53,54,58) suggested the Kruis symptoms score had an excellent positive predictive value with a pooled sensitivity of 77% and pooled specificity of 89%. Subsequently, an international working group developed the Rome criteria, which have undergone three iterations over 15 years. These criteria have been heavily promoted, although there has been only one study in which the accuracy of Rome I criteria has been evaluated and none describing the accuracy of Rome II or III (50). In the 602 patients studied, the Rome I criteria had a sensitivity of 71% and specificity of 85% (59).

All studies evaluating the accuracy of diagnostic criteria in patients with IBS face the problem of lack of a reference standard test for this condition. Notwithstanding, none of the symptom-based diagnostic criteria have an ideal accuracy and the Rome criteria, in particular, have been inadequately evaluated, despite their extensive use in the research setting. The ACG Task Force felt that a pragmatic definition that was simple to use and that incorporated key features of previous diagnostic criteria would be clinically useful. We, therefore, defined IBS as abdominal pain or discomfort that occurs in association with altered bowel habits over a period of at least three months.

Section 2.4 The role of alarm features in the diagnosis of IBS

Overall, the diagnostic accuracy of alarm features is disappointing. Rectal bleeding and nocturnal pain offer little discriminative value in separating patients with IBS from those with organic diseases. Whereas anemia and weight loss have poor sensitivity for organic diseases, they offer very good specificity. As such, in patients who fulfill symptom-based criteria of IBS, the absence

Table 2. Summary of diagnostic criteria used to define irritable bowel syndrome

Diagnostic criteria	Symptoms, signs, and laboratory investigations included in criteria
Manning (1978)	IBS is defined as the symptoms given below with no duration of symptoms described. The number of symptoms that need to be present to diagnose IBS is not reported in the paper, but a threshold of three positive is the most commonly used:
	1. Abdominal pain relieved by defecation
	2. More frequent stools with onset of pain
	3. Looser stools with onset of pain
	4. Mucus per rectum
	5. Feeling of incomplete emptying
	6. Patient-reported visible abdominal distension
Kruis (1984)	IBS is defined by a logistic regression model that describes the probability of IBS. Symptoms need to be present for more than two years.
	Symptoms:
	1. Abdominal pain, flatulence, or bowel irregularity
	2. Description of character and severity of abdominal pain
	3. Alternating constipation and diarrhea
	Signs that exclude IBS (each determined by the physician):
	1. Abnormal physical findings and/or history pathognomonic for any diagnosis other than IBS
	2. Erythrocyte sedimentation rate >20 mm/2 h
	3. Leukocytosis >10,000/cc
	4. Anemia (Hemoglobin < 12 for women or < 14 for men)
	5. Impression by the physician that the patient has rectal bleeding
Rome I (1990)	Abdominal pain or discomfort relieved with defecation, or associated with a change in stool frequency or consistency, PLUS two or more of the following on at least 25% of occasions or days for three months:
	1. Altered stool frequency
	2. Altered stool form
	3. Altered stool passage
	4. Passage of mucus
	5. Bloating or distension
Rome II (1999)	Abdominal discomfort or pain that has two of three features for 12 weeks (need not be consecutive) in the last one year:
	1. Relieved with defecation
	2. Onset associated with a change in frequency of stool
	3. Onset associated with a change in form of stool
Rome III (2006)	Recurrent abdominal pain or discomfort three days per month in the last three months associated with two or more of:
	1. Improvement with defecation
	2. Onset associated with a change in frequency of stool
	3. Onset associated with a change in form of stool

IBS, irritable bowel syndrome.

of selected alarm features, including anemia, weight loss, and a family history of colorectal cancer, inflammatory bowel disease, or celiac sprue, should reassure the clinician that the diagnosis of IBS is correct.

Patients with typical IBS symptoms also may exhibit so-called "alarm features" that increase concerns organic disease may be present. Alarm features include rectal bleeding, weight loss, iron deficiency anemia, nocturnal symptoms, and a family history

of selected organic diseases including colorectal cancer, IBD, and celiac sprue. Usually, it is recommended that patients who exhibit alarm features undergo further investigation, particularly with colonoscopy to rule out organic disease, e.g., colorectal cancer. The utility of this approach has been addressed in a systematic review of the literature (60). This review evaluated all patients presenting with lower gastrointestinal symptoms, as there was no study that specifically addressed IBS patients as a group. Nevertheless, the results of this review are likely to be applicable to IBS patients or may even overestimate the utility of alarm symptoms because abdominal pain (a defining symptom of IBS) is a negative predictor of serious underlying pathology (60). In 13 studies evaluating the diagnostic utility of abdominal pain in 19,238 patients, the pooled positive likelihood ratio was 0.72 (95% CI = 0.60–0.88), and the pooled negative likelihood ratio was 1.21 (95% CI = 1.11-1.32) for colorectal cancer, i.e., the presence of abdominal pain reduces the likelihood and the absence of pain increases the likelihood of colorectal cancer.

Our review on the utility of alarm features to diagnose colorectal cancer (1) identified 14 studies evaluating 19,189 patients with lower GI symptoms and reported on the accuracy of rectal bleeding in this regard. Rectal bleeding had a pooled sensitivity of 64% (95% CI = 55–73%) and pooled specificity of 52% (95% CI = 42–63%) for diagnosing colorectal cancer. Seven studies involving 4,404 patients evaluated the diagnostic utility of anemia and found a pooled sensitivity of 19% (95% CI = 5.5–33%) and pooled specificity of 90% (95% CI = 87–92%) for diagnosing colorectal cancer in patients with lower GI symptoms. There were five studies that assessed the accuracy of weight loss in 7,418 patients with lower GI symptoms. Weight loss had a pooled sensitivity of 22% (95% CI = 14–31%) and pooled specificity of 89% (95% CI = 81–95%).

It also has been suggested that the presence of nocturnal symptoms may identify a group of patients more likely to harbor organic disease. Studies suggest, however, that nocturnal abdominal pain is no more likely in patients with organic diseases than it is in in patients with IBS (61,62).

There is evidence to suggest that individuals with a family history of colorectal cancer, IBD, and celiac sprue are at higher risk of having these organic diseases. The increased risk of colorectal cancer among individuals with an affected first-degree relative under 60 years of age is well documented (63). There is epidemiologic evidence of a 4- to 20-fold increased risk of IBD disease in first-degree relatives of an affected patient (64). Recent evidence also has shown that between 4 and 5% of individuals with an affected first-degree relative will have celiac sprue (65).

Overall, the accuracy of alarm features is disappointing. Rectal bleeding and nocturnal pain offer little discriminative value in separating patients with IBS from those with organic diseases. Whereas anemia and weight loss have poor sensitivity for organic diseases, they offer very good specificity. As such, in patients who fulfill symptom-based criteria, the absence of selected alarm features, including anemia, weight loss, and a family history of colorectal cancer, IBD or celiac sprue, should reassure the clinician that the diagnosis of IBS is correct.

Section 2.5 The role of diagnostic testing in patients with IBS symptoms

Routine diagnostic testing with complete blood count, serum chemistries, thyroid function studies, stool for ova and parasites, and abdominal imaging is not recommended in patients with typical IBS symptoms and no alarm features because of a low likelihood of uncovering organic disease (Grade 1C). Routine serologic screening for celiac sprue should be pursued in patients with IBS-D and IBS-M (Grade 1B). Lactose breath testing can be considered when lactose maldigestion remains a concern despite dietary modification (Grade 2B). Currently, there are insufficient data to recommend breath testing for small intestinal bacterial overgrowth in IBS patients (Grade 2C). Because of the low pretest probability of Crohn's disease, ulcerative colitis, and colonic neoplasia, routine colonic imaging is not recommended in patients younger than 50 years of age with typical IBS symptoms and no alarm features (Grade 1B). Colonoscopic imaging should be performed in IBS patients with alarm features to rule out organic diseases and in those over the age of 50 years for the purpose of colorectal cancer screening (Grade 1C). When colonoscopy is performed in patients with IBS-D, obtaining random biopsies should be considered to rule out microscopic colitis (Grade 2C).

IBS is a disorder of heterogeneous pathophysiology for which specific biomarkers are not yet available. Diagnostic tests are therefore performed to exclude organic diseases that may masquerade as IBS and, in so doing, reassure both the clinician and the patient that the diagnosis of IBS is correct. Historically, IBD, colorectal cancer, diseases associated with malabsorption, systemic hormonal disturbances, and enteric infections are of the greatest concern to clinicians caring for patients with IBS symptoms. The broad differential diagnosis of IBS symptoms as well as medicolegal concerns related to making an incorrect diagnosis of IBS drives most clinicians to view IBS as a "diagnosis of exclusion". This practice has tangible consequences for patients, payors, and society at large. Physicians who feel that IBS is a diagnosis of exclusion order more diagnostic tests and spend more money to evaluate their patients than do experts who feel more confident about diagnosing IBS (66). Given this information, it is important to review the value of commonly ordered diagnostic tests in patients with suspected IBS, including complete blood count, serum chemistries, thyroid function studies, markers of inflammation, testing for celiac sprue, breath testing for lactose maldigestion and bacterial overgrowth, and colonic imaging.

When deciding on the necessity of a diagnostic test in a patient with IBS symptoms, one should consider first the pretest probability of the disease in question. If the pretest probability of a particular disease is sufficiently small, diagnostic testing directed at uncovering that improbable disease is unlikely to be either clinically useful or cost effective. Clinicians also should consider the performance characteristics (e.g., sensitivity,

Table 3. Prevalence of organic diseases in patients meeting symptom-based criteria for IBS

Organic GI disease	IBS patients (%)	General population (%)
Colitis/IBD[a]	0.51–0.98	0.3–1.2
Colorectal cancer[a]	0–0.51	0–6 (varies with age)
Thyroid dysfunction[b]	4.2	5–9
Gastrointestinal infection[b]	0–1.5	NA
Celiac sprue[b]	3.6	0.7
Lactose maldigestion[b]	38	26

[a]Data from Cash *et al.* (67). [b]Data courtesy of Moayyedi, *et al.* (personal communication, unpublished).

specificity, positive and negative predictive values) of the diagnostic test under consideration when deciding on its relative value. Data from systematic reviews that address the pretest probability of organic diseases in patients with IBS symptoms are presented in **Table 3**.

Application of the available data to routine clinical practice may be limited by a number of factors including the relatively small size of the study populations, the variable quality of study methodologies, and selected nature of study populations that typically derive from secondary or tertiary care facilities. Accepting these limitations, the prevalences of Crohn's disease, ulcerative colitis, colon cancer, and thyroid disease do not appear to be significantly different in patients with IBS symptoms compared with healthy controls. There is emerging evidence, however, to suggest that celiac sprue and lactose intolerance may be more prevalent in patients with IBS symptoms than in controls. Small Intestinal Bacterial Overgrowth (SIBO) continues to generate considerable interest as a possible cause of IBS symptoms, but this association remains highly controversial.

Patients who fulfill the symptom-based diagnostic criteria for IBS and who have no alarm features, require little formal testing before confidently arriving at the diagnosis of IBS. The likelihood of uncovering important organic diseases by complete blood count and serum chemistries is low and no greater in IBS patients than in healthy controls (67). Five studies have evaluated the utility of checking thyroid function in 2,160 IBS patients (68–72). The prevalence of abnormal thyroid function tests was 4.2% (range = 0–5.5%), a value very similar to that expected in the general population. Furthermore, in the infrequent cases in which abnormal test results have been identified, causality between the laboratory abnormality and the IBS symptoms has not been established. For these reasons, the routine application of thyroid function tests in IBS patients without alarm features is not recommended.

Similarly, stool for ova and parasite examination appears to offer little value in the evaluation of patients with IBS symptoms and no alarm features. Two trials have evaluated the yield of stool ova and parasite examination in IBS patients (69,70). One study of 170 patients with IBS found no abnormal stool ova and parasite examination results, whereas a second study in 1,154 patients reported an abnormal result in 1.6%. Symptom response following treatment of identified pathogens was not reported, so causality could not be established. Based on these results, the Task Force does not recommend the routine use of stool ova and parasite examination in patients with IBS.

There are very limited data on the utility of abdominal imaging tests in patients with IBS. One study evaluated the role of abdominal ultrasound to identify serious abdominal or pelvic pathology in 125 patients diagnosed with IBS by the Rome I criteria (73). Of these patients, 22 (18%) had abnormal ultrasound results, the most common explanation of which was gallstones in 6 (5%) patients. In no patient did the ultrasound results lead to a revision of the diagnosis of IBS. The Task Force recommends against the routine use of abdominal imaging in patients with IBS symptoms and no alarm features.

There is emerging evidence, however, to suggest that the prevalence of celiac sprue is higher among patients with IBS than in controls. The systematic review performed for this monograph (74) identified seven case-control studies (68,75–80) of 2,978 individuals (1,052 with IBS), which used anti-endomysial or tissue-transglutaminase antibodies to screen for celiac sprue. Three percent of the IBS cohorts, compared with 0.7% of controls, were found to have a positive anti-endomysial or transglutaminase antibody, or both (OR = 2.94, 95% CI = 1.36–6.35). In a separate analysis of five studies (68,76,78–80), 34 of 952 IBS patients compared wih 12 of 1,798 controls were found to have serologic (anti-gliadin, anti-endomysial, transglutaminase antibodies) and small bowel biopsy evidence of celiac sprue (3.6 vs. 0.7%; OR = 4.34, 95% CI = 1.78–10.6). Two decision analytic models have evaluated the cost effectiveness of serologic screening for celiac sprue in IBS patients and found that screening was cost effective as long as the prevalence of celiac sprue exceeded 1% (81,82). Based on the totality of evidence, the Task Force recommends routine serological screening for celiac sprue in patients with IBS-D and IBS-M.

Based on data from seven studies (83–89) of 2,149 IBS patients, the systematic review performed for this monograph reported the prevalence of lactose maldigestion by lactose breath testing to be 35% (95% CI = 17–56%). In a separate analysis of data from three case-control studies including 425 individuals (251 with IBS), lactose intolerance was found to be more prevalent in IBS patients than in controls (38 vs. 26%; OR = 2.57, 95% CI = 1.27–5.22). Unfortunately, these data, which suggest an association, do not prove causation between lactose maldigestion and IBS symptoms. It is worth noting that a substantial proportion of IBS patients have underlying abnormalities in intestinal and/or colonic motility and visceral sensation. Therefore, it is reasonable to speculate that the clinical consequences of lactose maldigestion may be greater in IBS patients than in controls (85). For these reasons, the Task Force suggests that providers question patients about a link

between lactose ingestion and their IBS symptoms. A food diary sometimes can help to identify such an association. If, after a careful history and review of a food diary, questions remain regarding the presence of lactose maldigestion, performance of a lactose hydrogen breath test can be considered (86). Whether other carbohydrates such as fructose and sucrose can cause or exacerbate IBS symptoms remains poorly defined.

A great deal of attention has been focused on the potential role of SIBO in the pathogenesis of IBS symptoms. Studies utilizing lactulose and glucose breath testing have yielded conflicting results. In the systematic review performed for this monograph, which included three studies (87–89) and 432 IBS patients, the prevalence of a positive lactulose breath test was 65% (95% CI = 47–81%). The corresponding prevalence using glucose breath testing (two studies with 208 patients) was 36% (95% CI = 29–43%) (90,91). The strikingly different results yielded by lactulose and glucose breath testing highlight the absence of a widely available gold standard to diagnose SIBO (86). In the only study performed to date that utilized lactulose breath testing, glucose breath testing, and jejunal aspiration for quantitative culture, no differences in the likelihood of abnormal test results were identified between IBS patients and controls. Quantitative increases in small bowel bacteria that did not meet the traditional diagnostic threshold for SIBO ($>10^5$ CFU/ml aspirate), however, were identified in the IBS cohort compared with controls (92). Although there seems little doubt that the intestinal and colonic microflora play a role in the pathogenesis of a subset of IBS patients, the Task Force feels that, currently, there is insufficient evidence to recommend breath testing for SIBO in patients with IBS.

Other diagnostic tests have been evaluated in IBS patients. One study utilized erythrocyte sedimentation rate and C-reactive protein to screen for evidence of systemic inflammation in 300 IBS patients (68). Three patients (1%) had an abnormal test and were subsequently diagnosed with organic disease. Fecal serine protease has been associated with activation of proteinase-activated receptors. Proteinase-activated receptors have been implicated in the development of visceral hypersensitivity in IBS patients. In a recent study, fecal serine-protease activity was assessed in 38 IBS patients, 15 patients with ulcerative colitis, and 15 healthy controls (93). Fecal serine protease activity was threefold higher in IBS-D patients than in controls or patients with nondiarrheal IBS; fecal serine protease levels also were elevated in the ulcerative colitis patients. More work is eagerly awaited to understand the role of these tests in patients with IBS symptoms.

Colonic imaging in an IBS patient with no alarm features is unlikely to reveal structural disease that might explain the patient's symptoms. In a recent systematic review, which included three studies and a total of 636 IBS patients, colonic imaging with colonoscopy or barium enema with or without flexible sigmoidoscopy, uncovered organic/structural disease in 1.3% (95% CI = 0.06–2.3%) (54,69,94). An interim analysis from a prospective, controlled, multicenter U.S. trial that compared the yield of colonoscopy in 216 IBS-D or IBS-M patients and 416 healthy controls undergoing colorectal cancer screening, found no difference in the prevalence of colorectal cancer (IBS = 0%, Controls = 0.2%) or IBD (IBS = 0.46%, Controls = 0%) among groups. The prevalence of adenomatous polyps (14 vs. 26%, $p = 0.0004$) and diverticulosis (13 vs. 21%, $p = 0.01$) was lower in the IBS cohort than in the healthy controls. These results may be confounded by the younger age (51 vs. 55 years, $p < 0.0001$) and greater proportion of women (69 vs. 42%, $p < 0.0001$) in the IBS cohort (95). Based on these results, the Task Force recommends that any patient older than 50 years of age with IBS symptoms should undergo colonic imaging for the purpose of colorectal cancer screening. Patients younger than 50 years of age who do not have alarm features need not undergo routine colonic imaging. Patients with IBS symptoms, who also present with alarm features, such as anemia or weight loss, should undergo colonic imaging to exclude organic disease, however, the clinician may feel that such an investigation can be deferred in some young patients with mild symptoms, e.g., a young woman with IBS symptoms and mild anemia where heavy periods may be the explanation.

In patients with symptoms consistent with IBS who also have alarm features, the nature and severity of symptoms as well as the patient's expectations and concerns influence the choice of diagnostic testing. Most patients will undergo routine blood and stool tests depending on their predominant symptoms. With regard to colonic imaging, it is appealing to suggest that patients with diarrhea-predominant symptoms undergo colonoscopy with inspection of the distal terminal ileum to exclude colon cancer and IBD respectively. The necessity of random colonic mucosal biopsies in patients with diarrhea-predominant symptoms remains controversial. As part of a recent prospective trial, random colonic mucosal biopsies were obtained at the time of colonoscopy in patients with IBS-D and IBS-M. Histologic evidence of microscopic colitis and nonspecific inflammation was found in 2.3 and 1.4% of IBS patients respectively; all of the patients with microscopic colitis had IBS-D (95). Combining the preceding evidence with a retrospective analysis that also identified an association between IBS-D and microscopic colitis (96) led the Task Force to recommend that if a patient with IBS-D has a colonoscopy, random colonic mucosal biopsies to exclude microscopic colitis should be considered. Clinical features suggestive of a secretory process, such as nocturnal diarrhea, large volume diarrhea that is unaffected by fasting, or a low fecal osmotic gap (< 50 Osm/kg), go against a diagnosis of IBS and strengthen the rational for obtaining random colonic biopsies to exclude microscopic colitis (97). If laboratory and/or stool testing suggest the presence of malabsorption, upper endoscopy with small bowel biopsies to further evaluate for celiac sprue or testing for SIBO may be warranted.

In patients with IBS-C who have alarm features, the major objective of colonic imaging is to exclude the presence of disease causing mechanical obstruction. Colonoscopy, virtual colonography, or barium enema can be used for this purpose.

Once the diagnosis of IBS has been established, clinicians should be reassured by the durability of the diagnosis. In two

studies with follow-ups ranging from three to more than 20 years, less than 1% of patients were given an alternative diagnosis felt to be responsible for their gastrointestinal symptoms (98,99).

Section 2.6 Diet and irritable bowel syndrome

Patients often believe certain foods exacerbate their IBS symptoms. There is, however, insufficient evidence that food allergy testing or exclusion diets are efficacious in IBS and their routine use outside of a clinical trial is not recommended (Grade 2C).

IBS patients often report that food intake exacerbates their symptoms. Surveys (100,101) suggest that 60–70% of IBS sufferers feel that their symptoms are related to food sensitivity and most exclude such offending foods from their diet (101). Clinicians also have explored whether dietary intervention can help alleviate symptoms in patients with IBS. Exclusion diets involve having the patient complete a food diary and then excluding those foods that seem to exacerbate symptoms. In addition, some researchers have excluded all dairy products, cereals, citrus fruits, potatoes, caffeine drinks, alcohol, additives, and preservatives (102), although mechanistic data supporting the omission of all these foods in the diet are meager. A systematic review (103) of the literature on food allergy in IBS identified eight studies (102,104–110) evaluating the response of 540 IBS patients to exclusion diets. Most studies were uncontrolled and the response rates to various exclusion diets ranged from 12.5 to 67% (**Figure 1**). Most of these papers claimed that such responses demonstrate the efficacy of exclusion diets in IBS, a conclusion that is difficult to interpret given the high placebo response that can be seen in this condition; more objective evidence is required before this conclusion can be accepted.

There is no gold standard test to diagnose food allergy (103). Skin prick tests and serum IgE or IgG levels to specific food antigens have been advocated, but all have uncertain sensitivity and specificity. Studies that have evaluated adverse food reactions in IBS patients have found no correlations between the types of food causing symptoms and the results of food allergy tests (100,111). This lack of correlation supports either a lack of accuracy of the diagnostic test or that food allergy is not a cause of IBS symptoms. The gold standard method of addressing this issue is the randomized controlled trial (RCT) and there are two such trials that gave patients with adverse food reactions a double-blind trial of the offending agent. In one study (104), patients correctly identified the offending food in 10 of 12 cases (83%), whereas the other study (105) essentially was negative. An additional trial (108) evaluated the efficacy of food elimination based on IgG antibody levels to a panel of 29 different food antigens. All IBS patients had food allergies according to this test and patients were randomized to an exclusion diet eliminating foods identified by allergy testing or a sham diet. The study reported that the food elimination diet was efficacious, however, analysis of the intention-to-treat or all-evaluable patient groups revealed that the impact was only modest: 18 of 65 (28%) patients responded in the elimination diet group compared with 11 of 66 (17%) in the sham diet group, ($p = 0.19$, not significant).

Even if exclusion diets are shown to have modest efficacy in ameliorating symptoms in patients with IBS, it will be difficult to determine whether such benefit resulted from a change in intraluminal end products of bacterial metabolism, an alteration in immunologically mediated food allergy or that the change in diet acted as a prebiotic to vary the intestinal microbiota (112,113). Currently there is little evidence to support exclusion diets for the treatment of IBS, although a modest effect cannot be excluded from these data. More RCTs are needed after carefully excluding patients with celiac sprue and lactose intolerance.

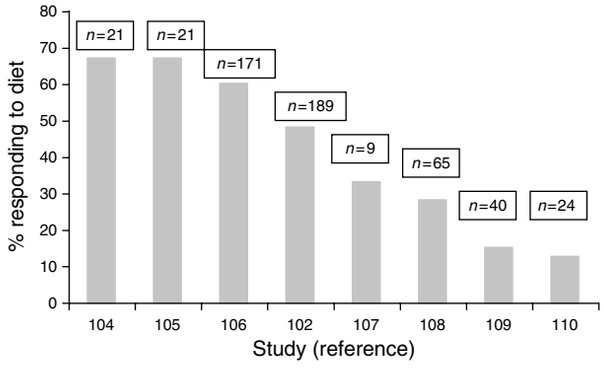

Figure 1. Proportion of irritable bowel syndrome (IBS) patients responding to exclusion diets.

Section 2.7 Effectiveness of dietary fiber, bulking agents, and laxatives in the management of irritable bowel syndrome

Psyllium hydrophilic mucilloid (ispaghula husk) is moderately effective and can be given a conditional recommendation (Grade 2C). A single study reported improvement with calcium polycarbophil. Wheat bran or corn bran is no more effective than placebo in the relief of global symptoms of IBS and cannot be recommended for routine use (Grade 2C). PEG laxative was shown to improve stool frequency—but not abdominal pain—in one small sequential study in adolescents with IBS-C (Grade 2C).

Most physicians recommend the use of dietary fiber or bulking agents to regularize bowel function and to reduce pain in patients with IBS. The quality of the evidence supporting this recommendation, however, is poor. Our systematic review (114) found 12 RCTs with global endpoints dealing with this issue (115–126). All but one were conducted outside of North America, most were over 15 years old and, therefore, tended to be small (in aggregate involving 591 subjects), had suboptimal experimental design, and utilized a variety of experimental agents and conditions. IBS-C was differentiated from IBS-D in only three studies; two of these recruited only IBS-C patients and in the other, almost half of the participants had IBS-C. The other nine studies did not specify which IBS subtypes were

included. Most studies did not use criteria-based diagnosis, concealed allocation, adequate blinding, or other methods now recommended in modern study design. Nine trials were double-blind, two were single-blind, and one was unblinded. Few were at least eight weeks in duration and none followed patients beyond the period of treatment.

Most studies we reviewed examined the effect of wheat bran or psyllium hydrophilic mucilloid (ispaghula husk). Taken as a group, treatment with wheat bran provided no global benefit in patients with IBS. Only one study (which did not include a placebo-controlled group) demonstrated improvement in pain frequency, severity and stool frequency with wheat bran (116), while the others showed no significant improvement with treatment. Overall, the relative risk of IBS symptoms not improving with wheat bran was 1.02 (95% CI = 0.82–1.27) (114). In contrast, global IBS symptoms were improved in four of the six studies with psyllium hydrophilic mucilloid. The relative risk of IBS symptoms not improving with psyllium hydrophilic mucilloid was 0.78 (95% CI = 0.63–0.96) (114). The NNT with psyllium hydrophilic mucilloid was six (95% CI = 3–50).

A single study of the effectiveness of corn fiber in patients with IBS showed no substantial benefit over placebo (127). IBS patients preferred calcium polycarbophil to placebo in another controlled trial (128).

Safety issues and adverse events were not addressed formally in these studies of bulking agents. Clinical studies and expert opinion suggest that increased fiber intake may cause bloating, abdominal distention, and flatulence, especially if increased suddenly (129,130). Gradual titration is advised if these agents are used.

Laxatives have not been studied in randomized, placebo-controlled trials in adults with IBS and have mostly been studied in patients with chronic constipation. A single small sequential study compared symptoms before and with PEG laxative treatment in adolescents with IBS-C (131). Stool frequency improved from an average of 2.07±0.62 bowel movements per week to 5.04±1.51 bowel movements per week ($p < 0.05$), but there was no effect on pain intensity.

Section 2.8 Effectiveness of antispasmodic agents, including peppermint oil, in the management of irritable bowel syndrome

Certain antispasmodics (hyoscine, cimetropium, and pinaverium) may provide short-term relief of abdominal pain/discomfort in IBS (Grade 2C). Evidence for long-term efficacy is not available (Grade 2B). Evidence for safety and tolerability are limited (Grade 2C). Although peppermint oil appears superior to placebo in IBS, this conclusion is based on a small number of studies (Grade 2B).

Based on clinical observations as well as some experimental evidence, it has long been postulated that IBS symptoms including pain, in particular, emanate from colonic smooth muscle spasm. A variety of agents, some acting directly on smooth muscle and others on cholinergic receptors, therefore, have been developed and tested in IBS over the decades. Notwithstanding the possibility that their actions may reside elsewhere, these agents generally have been referred to as "antispasmodics" and marketed as such.

Our systematic review (114) suggested that there is evidence for the efficacy of antispasmodics as a class in IBS, however, there are significant variations in the availability of these agents in different countries. For example, of the 22 separate studies identified (117,120,121,132–150), all but four (three trials using hyoscine (117,120,132), and one with dicyclomine (143)) involved drugs that are not available in the United States: otilonium (138,145,147,148), cimetropium (133,135), pinaverium (144,146,149), trimebutine (137,142), alverine (140), mebeverine (121), pirenzipine (139), prifinium (141), propinox (150), and a combination of trimebutine and rociverine (136). Furthermore, the preparation of hysocine used in reported trials differs from that currently available in the United States. Very few of the trials are recent (only three since 2000 (138,140,150)) and earlier trials vary considerably in terms of diagnostic criteria (only two (138,140) featured a standardized methodology, e.g., one of the Rome iterations), inclusion criteria, dosing schedule, duration of therapy, and study endpoints. Many are of poor quality with only three studies (132,138,140) including more than 100 subjects and only one utilizing a validated outcome measure to define improvement in IBS symptoms following therapy (140). The available data also do not permit ready identification of a likely responder to this class of drugs or a particular agent; for example, only six studies reported on subtype of IBS according to predominant stool pattern (133,134,136,137,141,146) and the vast majority of studies used a global endpoint rather than including results of individual symptoms, such as pain, which might be expected to respond to this drug class.

The 22 trials included 1,778 IBS patients and the relative risk of symptoms persisting with antispasmodics compared with placebo was 0.68 (95% CI = 0.57–0.81). The NNT to prevent IBS symptoms persisting in one patient was five (95% CI = 4–9).

Of all drugs studied, the most data were available for otilonium (138,145,147,148), trimebutine (136,137,142), cimetropium (133–135), hyoscine (117,120,132), and pinaverium (144,146,149). Trimebutine appeared to have no benefit over placebo in IBS, whereas the other four drugs all significantly reduced the risk of IBS patients remaining symptomatic with therapy. There was considerable heterogeneity, however, among individual trials, with each study only including a small number of patients. The best evidence for efficacy appears to exist for the use of hyoscine, the efficacy of which was studied in more than 400 patients with no statistically significant heterogeneity detected, and four (95% CI = 2–25) patients needing to be treated to prevent one patient's symptoms from persisting after completion of therapy.

Furthermore, the adverse event profile of these agents has not been defined adequately.

Thirteen studies reported on the total number of adverse events in 1,379 patients (121,132–138,140,142,143,147,149). The commonest adverse events were dry mouth, dizziness,

and blurred vision, and there were no serious adverse events reported in either treatment arm in any of the trials. The relative risk of experiencing adverse events with antispasmodics compared with placebo was 1.62 (95% CI = 1.05–2.50), with statistically significant heterogeneity detected among studies ($I^2 = 38\%$, $p = 0.07$). The NNH with antispasmodic drugs was 18 (95% CI = 7–217).

A variety of preparations containing various formulations of peppermint oil are available through conventional and complementary routes and have been used for some time on a largely empiric basis for the treatment of IBS-like symptoms. Limited experimental data suggest the ability of peppermint oil to relax smooth muscle, thus its inclusion in the same category as antispasmodics. Only four studies (151–154) were identified in a systematic review (114) comparing peppermint oil with placebo in 392 patients; all but one (154) were short-term and only one reported on the type of IBS patient according to stool pattern (153).

The relative risk of IBS symptoms persisting with peppermint oil compared with placebo was 0.43 (95% CI = 0.32–0.59), with statistically significant heterogeneity detected between studies ($I^2 = 31\%$, $p = 0.23$) (114). The NNT with peppermint oil to prevent one patient with IBS remaining symptomatic was 2.5 (95% CI = 2–3) (114). Only three studies reported adverse events data (152–154), and these were few in number.

Section 2.9 Effectiveness of antidiarrheals in the management of irritable bowel syndrome

The antidiarrheal agent loperamide is not more effective than placebo at reducing abdominal pain or global symptoms of IBS, but is an effective agent for treatment of diarrhea, improving stool frequency and stool consistency (Grade 2C). RCTs with other antidiarrheal agents have not been performed. Safety and tolerability data on loperamide are lacking.

Patients with IBS who have diarrhea display faster colonic transit than healthy subjects (155,156); therefore, agents that slow colonic transit may be beneficial in reducing symptoms. Loperamide is the only antidiarrheal agent sufficiently evaluated in RCTs for the treatment of diarrhea-predominant IBS.

There have been two RCTs involving 42 patients that evaluated the effectiveness of loperamide in the treatment of IBS with diarrhea-predominant symptoms (157,158). There were no statistically significant effects of loperamide on overall symptoms compared with placebo (relative risk of IBS symptoms not improving = 0.44; 95% CI = 0.14–1.42). Both trials were double-blinded, but neither reported adequate methods of randomization nor adequate concealment of allocation. The proportion of women in each trial was unclear. Both trials used a clinical diagnosis of IBS supplemented by negative investigations to define the condition. Both trials reported that 100% of the loperamide-treated group had improved stool consistency compared with 20–45% of controls ($p = 0.006$). The pooled analysis of stool frequency suggested that the relative risk of stool frequency not improving with loperamide was 0.2. (95% CI = 0.05–0.9). There were no adverse events in one study (157), and four adverse events in each arm of the other trial (158).

Section 2.10 Effectiveness of antibiotics in the management of irritable bowel syndrome

A short-term course of a nonabsorbable antibiotic is more effective than placebo for global improvement of IBS and for bloating (Grade IB). There are no data available to support the long-term safety and effectiveness of nonabsorbable antibiotics for the management of IBS symptoms.

Rifaximin, a nonabsorbable antibiotic, has demonstrated efficacy in three RCTs evaluating 545 IBS patients (159–162). All of these RCTs were well designed, meeting all criteria for appropriately designed RCTs (i.e., truly randomized studies with concealment of treatment allocation, implementation of masking, completeness of follow-up and intention-to-treat analysis) and meeting most criteria of the Rome committee for design of treatment trials of functional GI disorders (e.g., patients met Rome criteria for IBS, no placebo run-in, baseline observation of patients to assess IBS symptoms, and primary study outcome is improvement in global IBS symptoms) (163). All of these RCTs demonstrated statistically significant improvement in symptoms with rifaximin, and rifaximin-treated patients were 8–23% more likely to experience global improvement in IBS symptoms, bloating symptoms, or both compared with placebo-treated patients. Rifaximin is not FDA-approved for treatment of IBS, although it is FDA-approved for treatment of traveler's diarrhea at the dose of 200 mg twice daily for three days. However, IBS trials utilized higher doses of rifaximin for longer periods: 400 mg three times daily for 10 days (162,164), 400 mg twice daily for 10 days (161), and 550 mg twice daily for 14 days (159,160). The largest RCT ($n = 388$ patients) only examined IBS-D patients, and in this trial, rifaximin-treated patients demonstrated significant improvement in their diarrhea compared with placebo-treated patients (164). Based on these results, rifaximin is most likely to be efficacious in IBS-D patients or IBS patients with a predominant symptom of bloating and the appropriate dosage is approximately 1,100–1,200 mg/day for 10–14 days.

In the largest trial, 388 IBS-D patients were randomized to rifaximin 550 mg twice daily for two weeks followed by placebo for another two weeks or, alternatively, they took placebo for four weeks. In this trial, patients had to experience adequate relief of IBS symptoms in two of the three final weeks to be defined as a responder. Rifaximin-treated patients were significantly more likely to be responders (52.4 vs. 44.2%, $p = 0.03$). Notably, most of the improvement was not noted until after completion of the course of treatment. In a well-publicized RCT (162,164), 87 IBS patients were randomized to rifaximin 400 mg three times daily for 10 days or placebo with a 10-week follow-up period. In this study, severity of global IBS symptoms was based on a composite symptom score, and patients had to experience a 50% improvement in global IBS symptoms from baseline to one week after completion of antibiotics to be defined as a responder

(37.2 vs. 15.9%, $p < 0.05$). Based on assessment of the entire 10-week follow-up period, rifaximin-treated patients were significantly more likely than placebo-treated patients to experience 50% improvement in bloating (49.2 vs. 22.6%), diarrhea (50.6 vs. 35.3%), abdominal pain (39.7 vs. 28.9%), and constipation (35.1 vs. 28.1%) (164), although a separate mixed-model statistical analysis of the same data did not demonstrate significant improvement for the individual symptoms of diarrhea, abdominal pain, or constipation (162). Finally, another RCT examined 103 patients with a primary complaint of bloating, 70 of whom met Rome II criteria for IBS. Among IBS patients, rifaximin-treated patients were significantly more likely than placebo-treated patients to state that "symptoms have improved since starting the drug" after completion of study treatment (41 vs. 18%), but the percentage of patients who continued to state that "symptoms have improved since starting the drug" decreased 10 days after completion of study treatment in both groups (27 vs. 9%). This finding suggests that relief of IBS symptoms may not be durable after completion of antibiotics, although other RCTs (162,164) have demonstrated that IBS symptom improvement lasts for at least 10 weeks. Furthermore, an Italian study (165) examined 61 consecutive patients with positive lactulose hydrogen breath tests, who were treated with rifaximin 400 mg three times daily for seven days. These patients had repeat breath tests at three, six and nine months. Breath tests gradually became positive in a substantial proportion of patients at three months (13%), six months (28%), and nine months (46%), and recurrences of positive breath tests were associated with increases in abdominal pain, bloating, flatulence, and diarrhea, based on mean visual analog scale scores. Based on one open-label retrospective study, IBS patients with recurrent symptoms respond to repeated courses of rifaximin (166).

Among other antibiotics, a single RCT (167) of 111 patients demonstrated that neomycin-treated patients were more likely to experience 50% improvement in global IBS symptoms compared with placebo-treated patients (43 vs. 23%, $p < 0.05$). One trial of clarithromycin (168) did not assess efficacy of antibiotics for IBS as a primary outcome. In this trial, a cohort of 40- to 49-year-old individuals was screened for *Helicobacter pylori*. If an individual was positive for *H. pylori*, then he/she received clarithromycin, omeprazole and tinidazole, or placebos for one week. As part of this study, patients also completed gastrointestinal symptom questionnaires at baseline, six months and two years, and IBS was defined as presence of three or more Manning criteria. Among 274 participants with IBS at baseline, 42% of the antibiotic group and 42% of the placebo group had IBS two years after their one-week course of treatment. Finally, one trial (169) reported that metronidazole was more effective than placebo at improving global IBS symptoms, but this study did not present data that were extractable.

No study reported on overall adverse events, but all stated that antibiotics were well tolerated with no severe adverse events. Two trials assessing rifaximin (159,160,162,164) provided data on individual adverse events, and no significant differences in individual adverse events were noted between rifaximin-treated and placebo-treated patients.

Overall, rifaximin consistently demonstrates improvement in global IBS symptoms and bloating in well-designed trials. The majority of patients in rifaximin trials had IBS-D. Therefore, rifaximin is most likely to be beneficial in IBS-D patients or IBS patients with bloating as their primary symptom. The most appropriate dose of rifaximin for IBS is unclear. Based on currently available data, 400 mg three times a day for 10–14 days is efficacious. IBS symptom relief appears to last for 10–12 weeks, but symptoms may recur over three to nine months. Neomycin also demonstrated efficacy in a single, small RCT of IBS patients. Adverse events were not more common in antibiotic-treated than placebo-treated patients. However, given the often chronic and recurrent nature of IBS symptoms and the theoretical risks related to long-term treatment with any antibiotic, a recommendation regarding continuous or intermittent use of this agent in IBS must await further, long-term studies. It must also be stressed that available data on rifaximin is based on phase II studies; phase III studies have yet to be reported.

Section 2.11 Effectiveness of probiotics in the management of irritable bowel syndrome

In single organism studies, lactobacilli do not appear effective; bifidobacteria and certain combinations of probiotics demonstrate some efficacy (Grade 2C).

Probiotics have been used on an empiric basis for many years in the treatment of IBS, although recent interest in the science of the intestinal flora (microbiota) and probiotics, and our increasing awareness of putative factors in IBS pathophysiology, such as exposure to enteric pathogens, qualitative and quantitative changes in the enteric flora, and subtle levels of colonic inflammation or immune activation, have stimulated more extensive studies of the use of these preparation in IBS.

Our systematic review (170) identified 19 studies (171–189) including a total of 1,668 participants that were deemed eligible. The quality of studies was reasonable with nine (173,174,178, 180,181,183,187–189) reporting an adequate method of randomization and six (173,174,181,183,187,189) describing appropriate methods of concealment of allocation. All but three (175,176,184) recruited patients according to Rome or Manning criteria.

Eleven trials (173,175–177,180–182,186–189) evaluated 936 participants and reported IBS symptoms as a dichotomous outcome. Taken as a group, probiotics had a statistically significant effect to reduce IBS symptoms (RR symptoms persisting in probiotic group = 0.71; 95% CI = 0.57–0.87) with an NNT of four (95% CI = 3–12.5). These data probably overestimate the effects of probiotics, however, as there was heterogeneity and evidence of funnel asymmetry, suggesting there may be publication bias with an overrepresentation of small positive studies in the published literature. Furthermore, higher quality studies reported a more modest treatment effect compared with lower quality trials. There was no difference among the different types of

probiotics used, with *Lactobacillus* (175–177,189), *Bifidobacterium* (186,187), *Streptococcus* (188), and combinations of probiotics (173,180–182) all showing a trend toward benefit.

Fourteen publications (171–174,177–185,187) with 1,351 participants reported IBS symptoms as a continuous variable. Probiotics had a statistically significant effect to improve IBS symptoms compared with placebo (standardized mean difference = −0.34; 95% CI = −0.60 to −0.07). Four trials (172,177–179) evaluated *Lactobacillus* in 200 patients and found no effect on IBS symptoms. Nine trials (171,173,174,180–185) evaluated combinations of probiotics in 772 patients with a significant effect in improving IBS symptoms, whereas two trials (178,187) evaluated *Bifidobacterium* in 379 patients with a trend toward improving IBS symptoms.

The main limitation of this review is that there were a variety of species, strains, and doses of probiotics used and, therefore, it was difficult to reach a conclusion about the optimal probiotic strategy to use in patients with IBS. Data from this review are conflicting. The dichotomous data suggest that all probiotic therapies show a trend for being efficacious in IBS. In contrast, the continuous data suggest (1) *Lactobacilli* have no impact on symptoms; (2) probiotic combinations improve symptoms in IBS patients; and (3) there was a trend for *Bifidobacteria* to improve IBS symptoms. The review was conservative as we decided *a priori* to include all doses of probiotics. One trial (187) of *Bifidobacterium infantis* 35624 was a dose-ranging study in which the authors found on *post hoc* evaluation that the preparation methods had resulted in the higher dose of organisms being clumped together and inactivated. This dose was still included in the analysis, but had it been excluded, the *Bifidobacteria* data would have reached statistical significance. Almost all probiotic combinations contained both *Bifidobacteria* and *Lactobacilli* and the latter did not have an effect in the continuous data meta-analysis. It is therefore possible that *Bifidobacteria* are the active agent in probiotic combinations. Alternatively, it is possible that different species of probiotics are synergistic in promoting a therapeutic effect on IBS.

Section 2.12 Effectiveness of the $5HT_3$ receptor antagonists in the management of irritable bowel syndrome

The 5-HT_3 receptor antagonist alosetron is more effective than placebo at relieving global IBS symptoms in male (Grade 2B) and female (Grade 2A) IBS patients with diarrhea. Potentially serious side effects including constipation and colon ischemia occur more commonly in patients treated with alosetron compared with placebo (Grade 2A). The benefits and harms balance for alosetron is most favorable in women who have not responded to conventional therapies (Grade 1B). The quality of evidence for efficacy of 5-HT_3 antagonists in IBS is high.

A number of drugs targeting serotonin receptors have demonstrated efficacy for improving global symptoms in IBS patients. Serotonin has been found to play key roles in the physiology of the GI tract in health and disease. Approximately 95% of the body's serotonin (5-hydroxytryptamine; 5-HT) is found in the GI tract, the largest proportion of which is present in the enterochromaffin cells. When released, serotonin can interact with a number of different 5-HT receptors, the 5-HT_1, 5-HT_3, and 5-HT_4 receptor subtypes playing major roles in GI motor/secretory function and visceral sensation (190). 5-HT_3 receptor antagonists delay GI transit, reduce colonic tone, blunt the gastrocolic reflex and decrease visceral sensation (190–193), making members of this drug class potentially attractive as a treatment for patients with IBS-D.

Alosetron originally was approved for the treatment of women with IBS-D in the United States in February 2000**.** In the systematic review commissioned to assist the development of this guideline (194), eight placebo-controlled trials were found that evaluated alosetron use in 4,987 patients (195–202). Considering the primary therapeutic endpoint as "adequate relief" of abdominal pain and discomfort or urgency, the relative risk of IBS persisting with alosetron treatment was 0.79 (95% CI = 0.69–0.90 with NNT = 8; 95% CI = 5–17). In a comparative trial, alosetron also proved superior to the antispasmodic medication mebeverine in female patients with nonconstipating IBS (203).

Studies have consistently shown benefits of alosetron for global and individual symptoms in female patients with IBS-D. One randomised, double-blind, placebo-controlled study of women with IBS-D established that patient satisfaction was significantly greater with alosetron compared with placebo for overall symptom relief (69 vs. 46%, $p < 0.001$) as well as for the relief of urgency, speed of relief, time to return of normal activities, relief of abdominal pain, and prevention of return of urgency (204). In another placebo-controlled study, alosetron demonstrated sustained relief of abdominal pain and discomfort as well as urgency in IBS-D patients for up to 48 weeks with a safety profile comparable to that of placebo (200). A randomized, placebo-controlled trial also found alosetron to be effective in men with IBS-D. (201) In this phase II dose-ranging study, 1 mg of alosetron taken twice daily resulted in adequate relief of abdominal pain and discomfort in 53% of men with IBS-D compared with 40% of men given placebo ($P < 0.001$).

The three trials of cilansetron evaluating a total of 2,229 IBS patients (205–207) were also identified in the systematic review (194). Cilansetron 3 mg twice daily was statistically significantly superior to placebo (RR of symptoms persisting = 0.75; 95% CI = 0.69–0.82), with an NNT of six (95% CI = 5–8). Cilansetron is not available in any country and is unlikely to be marketed in view of the adverse event data seen with alosetron.

Unfortunately, alosetron has been linked to the development of severe constipation and colon ischemia in a small percentage of patients. In the systematic review conducted for this guideline, seven studies (196–202) were identified that presented overall adverse event data in 4,609 patients. Patients randomized to receive alosetron were statistically significantly more likely to report an adverse event than were those randomized to placebo (RR of adverse event = 1.18; 95% CI = 1.08–1.29). The NNH with alosetron was 10 (95% CI = 7–16). Constipation was the most commonly reported adverse event with alosetron, and its development appeared to be dose-dependent (1 mg

twice daily = 29%; 0.5 mg twice daily = 11%). The risk of ischemic colitis was independent of dose. A systematic review of the clinical and postmarketing surveillance data from IBS patients and the general population confirmed a greater incidence of severe complicated constipation and ischemic colitis in patients taking alosetron (208), however, the incidence of these events was low, with a rate of 1.1 cases of ischemic colitis and 0.66 cases of complicated constipation per 1,000 patients-years of alosetron use.

Because of these rare but serious side effects, alosetron was voluntarily withdrawn by GlaxoSmithKline from the U.S. marketplace in November 2000. In June 2002, the FDA approved the re-release of alosetron for use in female patients with chronic, severe IBS-D who had failed to respond to conventional therapy. Current use of alosetron is regulated by a prescribing program set forth by the FDA and administered by the manufacturer (Prometheus Laboratories, San Diego, CA). The recommended starting dose of alosetron is 0.5 mg twice daily. This lower dose of alosetron is supported by results from a randomized, double-blind, placebo-controlled trial involving 705 women with severe IBS-D who were randomized to alosetron or placebo (202). Alosetron proved more effective for global IBS symptoms at doses of 0.5 mg/day (50.8%), 1 mg/day (48%), and 1 mg twice daily (42.9%) than placebo (30.7%, $p < 0.02$ for all comparisons). Constipation was dose dependent, reported by 9, 16, and 19% of patients randomized to 0.5 mg/day, 1 mg/day, or 1 mg twice daily, respectively. One case of ischemic colitis was reported in the 0.5 mg/day group and one case of fecal impaction was reported in the 1 mg twice daily group. If after four weeks, the drug is well tolerated but the patient's IBS-D symptoms are not adequately controlled, the dose can be increased to 1 mg twice daily. Alosetron should be discontinued if a patient develops symptoms or signs suggestive of severe constipation or ischemic colitis or if there is no clinical response to the 1 mg twice daily dose after four weeks. Alosetron is contraindicated in patients with significant liver disease and has been designated as a pregnancy category B drug.

Section 2.13 Effectiveness of $5HT_4$ (serotonin) receptor agonists in the management of irritable bowel syndrome

The 5-HT_4 receptor agonist tegaserod is more effective than placebo at relieving global IBS symptoms in female IBS-C (Grade 1A) and IBS-M patients (Grade 1B). The most common side effect of tegaserod is diarrhea (Grade 1A). A small number (0.11%) of cardiovascular events (myocardial infarction, unstable angina, or stroke) were reported among patients who had received tegaserod in clinical trials.

Tegaserod was the only 5-HT_4 agonist that had been approved for the treatment of IBS, but it was withdrawn from the market in March 2007 because of a low rate (0.11%) of cardiovascular events in tegaserod-treated patients.

A systematic review (209) identified multiple RCTs evaluating the efficacy of tegaserod in over 9,000 patients with IBS-C or IBS-M (210–219). The dose of tegaserod used ranged from 1 mg to 12 mg twice daily, and duration of therapy from two to 20 weeks. Almost all RCTs, however, assessed tegaserod at a dose of 6 mg twice daily for 12 weeks. All trials recruited only women or mostly women. Therefore, tegaserod was approved only for the treatment of IBS-C in women, and the recommendations in this guideline should only be applied to female IBS patients. Review of material submitted to the FDA reveals that these RCTs (210–219) met criteria for an appropriately designed RCT (i.e., truly randomized studies with concealment of treatment allocation, implementation of masking, completeness of follow-up and intention-to-treat analysis) and met almost all criteria of the Rome committee for design of treatment trials of functional GI disorders (e.g., patients met Rome criteria for IBS, no placebo run-in, treatment duration of eight to 12 weeks, baseline observation of patients to assess IBS symptoms, primary study outcome is improvement in global IBS symptoms, sample size calculation is provided and adequate sample size is enrolled, etc.).

In our meta-analysis, tegaserod 6 mg twice daily was significantly more effective than placebo for satisfactory improvement of global IBS symptoms (relative risk of IBS not improving = 0.85; 95% CI = 0.80 to 0.90), however, there was significant heterogeneity in results, suggesting that treatment populations (IBS-C vs. IBS-M), study endpoints or study design were too different to justify combining the results. In individual RCTs, tegaserod-treated patients were 5–19% more likely than placebo-treated patients to achieve satisfactory relief of global IBS symptoms, and tegaserod-treated patients were significantly more likely to experience improvement in abdominal discomfort, satisfaction with bowel habits, and bloating in most RCTs. Also, tegaserod is the only $5HT_4$ agonist that has been evaluated and fully reported in an IBS-M population. In a well-designed RCT (218), of IBS-M and IBS-C patients, those treated with tegaserod were 15% more likely to demonstrate improvement in global IBS symptoms compared with placebo-treated patients.

Neither renzapride nor cisapride are marketed for use in North America, although cisapride may be obtained through a complicated compassionate use drug protocol. Indeed these drugs are not available in most developed countries; we still conducted a systematic review of their efficacy to establish whether other drugs in this class had a role in IBS. There were four RCTs randomizing 317 IBS-C patients to either cisapride or placebo (220–223). All studies used a dose of 5 mg three times daily for 12 weeks, titrating up to 10 mg three times daily at four weeks if there was no response to therapy and there was no significant benefit compared with placebo (RR of symptoms persisting = 0.91; 95% CI = 0.58–1.43, $I^2 = 70\%$). We identified three trials of renzapride in 726 Rome II IBS patients (224–226). The trials used 1–4 mg of renzapride once daily for a duration of up to 12 weeks and there was no significant benefit compared to placebo (RR of symptoms persisting = 0.99; 95% CI = 0.79–1.23, $I^2 = 48\%$). In April 2008, Alizyme Pharmaceuticals (Cambridge, UK), manufacturer of renzapride, announced that they had discontinued development of renzapride for IBS-C because of disappointing Phase III trial results that showed only limited clinical improvement

compared with the placebo for the primary study endpoint (~0.45 months of IBS symptom relief vs. 0.55–0.60 months of symptom relief in a three-month trial) and that the efficacy was not sufficient to justify further development.

Total numbers of patients experiencing adverse events were reported in only three tegaserod trials, containing 2,827 patients (212,215,218). There was no statistically significantly increased risk of overall adverse events detected with tegaserod (RR = 1.07; 95% CI = 0.99–1.15, $I^2 = 0\%$) and 48% of the tegaserod arm and 45% of the placebo arm reported at least one adverse event. Diarrhea occurred significantly more often in the tegaserod-treated patients than in the placebo-treated patients with most individual RCTs reporting diarrhea in approximately 10% of the former group and 5% of the latter group. Approximately 1–2% of tegaserod-treated patients discontinued tegaserod because of severe diarrhea.

Tegaserod was withdrawn from the market in March 2007 after data from the entire clinical trial database of 29 RCTs were presented to the FDA (227). There were 11,614 patients treated with tegaserod and 7,031 treated with placebo; the average age of study subjects was 43 years, and 88% were women. Cardiovascular events occurred in 0.11% of tegaserod-treated patients vs. 0.01% of placebo-treated patients. Thirteen tegaserod-treated patients had myocardial infarction ($n = 4$), unstable angina ($n = 6$), or stroke ($n = 3$) whereas one placebo-treated patient had a transient ischemic attack. Currently, tegaserod is not available under any treatment investigational drug protocol, but it is available through the FDA under an emergency investigational drug protocol.

Serious cardiac arrhythmias including ventricular tachycardia, ventricular fibrillation, torsades de pointes, and QT prolongation have been reported in patients taking cisapride, especially those using medications that increase cisapride blood levels by inhibiting the cytochrome P450 3A4 enzymes that metabolize cisapride, e.g., clarithromycin, erythromycin, troleandomycin, nefazodone, fluconazole, itraconazole, ketoconazole, indinavir, and ritonavir. As a result of these adverse events reports, cisapride was withdrawn from the US market in July 2000, but is still available under a compassionate-use protocol from the FDA.

Overall, tegaserod consistently demonstrates efficacy for global IBS symptom improvement and individual IBS symptom improvement in women with IBS-C based on well-designed trials. However, cisapride is only available under an emergency investigational drug protocol through the FDA. Cisapride has not demonstrated improvement compared with placebo. The development of renzapride was discontinued because of disappointing Phase III trial results about the magnitude of improvement with this treatment. Therefore, effective 5-HT_4 agonists for the management of IBS are not readily available.

Section 2.14 Effectiveness of the selective C-2 chloride channel activators in the management of irritable bowel syndrome

Lubiprostone in a dose of 8 μg twice daily is more effective than placebo in relieving global IBS symptoms in women with IBS-C (Grade 1B).

Lubiprostone is the only selective C-2 chloride channel (ClC-2) activator available worldwide. The drug works from the luminal surface to promote chloride secretion into the intestine. Chloride channels are proteins inserted into cell membranes to permit chloride ions to cross the otherwise impermeable cell membrane (228,229). Because intracellular chloride concentration is higher than that in the lumen due to the effect of a basolateral Na-K-2Cl pump, activation of an apical chloride channel in the intestinal epithelium results in chloride secretion (230). In the small intestine, sodium enters the lumen through the paracellular pathway in response to the negative charge of the secreted chloride ion and water follows passively. Thus the net effect of activation of a chloride channel is secretion of salt water into the lumen of the intestine.

Activation of the cystic fibrosis transmembrane regulator (CFTR), a high-capacity chloride channel inserted into the apical membrane of enterocytes, is responsible for many secretory diarrheas, such as cholera (231). The C-2 chloride channel is a lower capacity chloride channel that is thought to be more involved with the physiologic regulation of paracellular permeability and intracellular volume (229). No disease states have yet been associated with activation of this channel in humans.

Although lubiprostone is derived from prostaglandin, it does not work exclusively via prostaglandin receptors (232,233). It is poorly absorbed into the systemic circulation and appears to work topically in the small intestine. Lubiprostone is thought also to stimulate colonic motility by increasing intraluminal volume or by some additional as yet unknown mechanisms.

Lubiprostone has shown efficacy in RCTs in patients with chronic idiopathic constipation at a dose of 24 μg twice daily (234–236). Subgroup analysis of patients entered into those trials who had severe abdominal discomfort suggested some improvement in abdominal pain and prompted further study of lubiprostone in patients with IBS-C (237).

Dose-ranging studies showed effectiveness in reducing abdominal discomfort from IBS-C in doses ranging from eight to 24 μg twice daily (238). Side effects were greater at the higher doses so the 8 μg twice daily dose was selected for further testing in large RCTs lasting 12 weeks (239). These studies used a complicated end point designed to minimize placebo response rates. To be counted as an overall responder, subjects were asked to rate their responses each week on a seven-point balanced Likert scale ranging from "significantly worse" to "significantly relieved". Only those responding with "significantly relieved" for at least two of four weeks or "moderately relieved" for four of four weeks and who did not increase their use of relief medications and who did not have any weekly ratings of "moderately worse" or "significantly worse" were counted as monthly responders. Only those who were monthly responders for two of three months were counted as overall responders.

Placebo response for the pooled Phase III studies was only 10%. Subjects treated with lubiprostone 8 μg twice daily had a response rate of 18% ($p < 0.001$) (239). As most participants in these studies were women, FDA approval was granted only

for women with IBS-C. Factor analysis was applied to understanding whether improvement in one symptom drove the overall response rate to lubiprostone. Improvement in no individual symptom (e.g., constipation severity) was responsible for the overall response, suggesting that improvement in symptoms across the board was associated with global response (240). Quality of life also was investigated in these subjects. Lubiprostone treatment was associated with improvement in domains of health worry ($p < 0.025$) and body image ($p < 0.015$) (241).

Two continuation studies were done as part of the Phase III investigations in IBS-C. In the first, those who had received lubiprostone in the initial double-blinded 12-week study improved their response rate from 15 to 37% during the extension study (242). Patients initially receiving placebo increased their response rate from 8 to 31%. In the second continuation study, subjects initially treated with lubiprostone either were continued on therapy or therapy was withdrawn and subjects were followed for an additional four weeks (243). There was no difference in response rates between lubiprostone- and placebo-treated subjects at the end of this extension study. This study shows that there is no rebound of symptoms and there may be positive "carry over" effect after treatment.

No electrocardiographic changes were found during initial dose-ranging studies and with acute doses of up to 144 μg (244,245). Pooled analysis of studies using 24 μg twice daily showed no change in serum electrolytes (246). Analysis of all phase II and III studies using 24 μg twice daily dose in patients with chronic constipation for up to 48 weeks showed that the most common side effects were nausea (31%), diarrhea (13%), and headache (13%) (247). Abdominal pain, abdominal distention, and flatulence also were seen in >4% of subjects treated for chronic constipation. Nausea was less common in men (8%) and in the elderly (19%). Side effects were less frequent in Phase III studies of patients with IBS-C given 8 mg twice daily and included nausea (8%), diarrhea (6%), and abdominal pain (5%) (239). Postmarketing reports include allergic reactions and troubling dyspnea occurring within an hour of the first dose and generally resolving within three hours; this may recur with repeat dosing. Dyspnea was noted in 2.5% of chronic constipation patients treated with 24 mg twice daily and in 0.4% of IBS-C patients treated with 8 μg twice daily in the clinical trials (248).

Lubiprostone has been given a pregnancy category C rating. Animal studies showed no teratogenicity with even large doses and three of four animal species had no excess fetal loss when dosed during gestation (248). Guinea pigs had an excess rate of fetal resorption when dosed during pregnancy and this led to the recommendation that women who can have children have a pregnancy test before starting therapy and practice contraception while taking lubiprostone. Six women became pregnant during clinical trials with lubiprostone; four delivered healthy children, one was lost to follow-up, and one pregnancy was terminated electively (248). There is no information about use of lubiprostone in nursing mothers.

The FDA lists mechanical gastrointestinal obstruction as a contraindication to use of lubiprostone and advises that patients with symptoms suggesting obstruction should be evaluated before starting treatment (248).

Section 2.15 The effectiveness of antidepressants in the management of irritable bowel syndrome

TCAs and SSRIs are more effective than placebo at relieving global IBS symptoms, and appear to reduce abdominal pain. There are limited data on the safety and tolerability of these agents in patients with IBS (Grade 1B).

Patients with IBS that fails to respond to peripherally acting agents often are considered for treatment with antidepressants, especially if abdominal pain is a prominent symptom; the data on efficacy of antidepressants in IBS, however, has been questioned (249). In the largest, high-quality RCT, desipramine was tested against placebo in 216 patients with moderate-to-severe IBS (250); 90% of patients included had IBS according to a physician diagnosis and 80% fulfilled the Rome I criteria for IBS. Desipramine was begun at a starting dose of 50 mg, increased to 150 mg daily (an antidepressant dose) over a three-week interval, and then continued for a total of 12 weeks. By 12 weeks, 60% of patients responded to desipramine compared with 47% of those on placebo; this difference failed to reach significance in the intention-to-treat analysis. The definition of a responder was based on a measurement of patient satisfaction with the treatment rather than on a symptom evaluation; when individually analyzed, global well being and average daily abdominal pain scores were not significantly different between the desipramine and placebo groups. Overall, 28% of subjects treated with desipramine dropped out of the trial, most often because of side effects (250). Additional analyses from this trial suggest that a TCA, specifically desipramine, may be particularly useful in patients with IBS-D, likely because of the anticholinergic effect that characterizes this class of agents; the other trials evaluated did not prespecify IBS subgroup analyses (251). The presence of comorbid depression did not predict response to therapy (251).

Physicians often prefer to use a SSRI rather than a TCA because of the lower side-effect profile. The use of SSRIs in IBS is more controversial, however, because convincing evidence of efficacy from individual trials has been lacking (249). A systematic review on antidepressants in functional gastrointestinal disorders concluded that antidepressants were efficacious in IBS, but data on SSRIs were not included (252).

Antidepressants could theoretically provide a benefit in IBS by both central and peripheral mechanisms (253,254). SSRIs have effects on the gastrointestinal tract that differ from those of TCAs. For example, fluoxetine has been shown to decrease orocecal and whole gut transit times in both constipation-predominant IBS and controls (255). In contrast, the TCA imipramine has been shown to prolong orocecal and whole gut transit times in controls and in patients with IBS-D (255). Venlafaxine (an inhibitor of serotonin and norepinephrine reuptake) has been shown to reduce colonic compliance and relax the colon in healthy volunteers (256), whereas fluoxetine

and citalopram did not change colonic compliance or visceral hypersensitivity (257). Antidepressants are often prescribed when abdominal pain is a prominent feature, and it has been presumed any benefit is from a central antinociceptive effect.

We conducted a systematic review of the literature (258) and identified 13 RCTs that evaluated either TCAs or SSRIs in 789 patients (120,250,257,259–268). Global symptoms were significantly more likely to improve with an antidepressant, regardless of type (RR of IBS symptoms not improving = 0.66, 95% CI = 0.57–0.78), and there was only marginal statistically significant heterogeneity, so pooling of these data appears reasonable. TCAs were superior to placebo in pooled data from nine trials involving 575 IBS patients, with a NNT of 4 (95% CI = 3–8; RR of IBS not improving = 0.68, 95% CI = 0.56–0.83) (258). Overall, there were five trials evaluating SSRI therapy in 230 IBS patients and data suggested that this class of drugs also is efficacious in IBS with a NNT of 3.5 (95% CI = 2–14; RR of IBS not improving = 0.62, 95% CI = 0.45–0.87) (258). These drugs also have the advantage of being potentially better tolerated than TCAs (249), and because the SSRIs have a prokinetic effect (255), this drug class may work better in IBS-C than in those with IBS-D, although the studies performed did not actually evaluate this issue to confirm this clinical impression. Nevertheless, the data indicate that both TCAs and SSRIs appear able to improve global IBS symptoms. It was not possible to show a pooled benefit for individual symptoms because few trials reported them in detail, and not all trial participants had all of the key symptoms at study entry. In two of the trials, abdominal pain was the primary endpoint and a benefit was observed (259,265).

Data on safety of antidepressants was reported in six IBS trials involving 301 patients (257,259–262,267). The results suggested an increased risk in overall adverse events in those taking antidepressants but this did not reach statistical significance (RR adverse event with antidepressants = 1.63, 95% CI = 0.94–2.80). Given the limited data available on the safety and tolerability of antidepressants in IBS, we evaluated other diseases in which these drugs are used and found that this has been assessed in a systematic review of neuropathic pain (269). The NNH for major adverse effects, defined as an event leading to withdrawal, was 28 (95% CI = 17.6–68.9) for amitriptyline and 16.2 (95% CI = 8–436) for venlafaxine (269).

Head-to-head trials of a low-dose TCAs with an SSRI in IBS are also not available, and the long-term outcome of such therapies is relatively poorly documented, representing major gaps in the literature that remain to be filled.

Section 2.16 The effectiveness of psychological therapies in the management of irritable bowel syndrome

Cognitive behavioral therapy, dynamic psychotherapy, and hypnotherapy but not relaxation therapy are more effective than usual care in relieving global symptoms of IBS (Grade 1C).

Psychological therapies include cognitive behavioral therapy, relaxation therapy, hypnosis, and psychotherapy. Expert opinion supports the efficacy of psychological therapies although their benefits in IBS remain poorly quantified (270). A systematic review evaluating psychological therapies in IBS identified 17 studies, 10 of which had extractable data; 9 of the 10 studies, however, emanated from a single center (271). Two other reviews on the subject concluded that the quality of the available evidence was low and that these approaches were efficacious for individual IBS symptoms, but a meta-analysis was not undertaken (1,2). A Cochrane Collaboration systematic review of the efficacy of hypnotherapy identified four trials but the data were not combined (272).

The Task Force (273) identified 20 RCTs, making 21 different comparisons (250,274–292), including 1,278 IBS patients. There was a benefit of psychological therapy over usual care (RR of IBS not improving = 0.67, 95% CI = 0.57–0.79; NNT = 4; 95% CI = 3–5), however, there was significant heterogeneity so pooling these studies needs to be interpreted very cautiously. Nine of these studies came from the same US research group (274,275,277,282,285–287,289,292) and overall study quality was judged to be low. Relaxation therapy alone (282–285,291) had no significant benefit. Cognitive behavioral therapy (250,274–278,291), dynamic psychotherapy (280,281), and multicomponent psychological therapy (279,286,287) were all similarly efficacious when pooled separately. Two additional studies evaluated the global efficacy of hypnotherapy in IBS and overall reported a significant benefit with no significant heterogeneity (RR of IBS not improving = 0.48, 95% CI = 0.26–0.87; NNT = 2) (289,290). Other clinical trial evidence that could not be included in the pooled analyses because global efficacy was not assessed also favored hypnotherapy (293).

Overall, the data suggest that regardless of the type of psychological therapy applied, it was superior to usual care in terms of global symptom improvement (aside from relaxation therapy). None of the trials reported any adverse events with psychological therapy although, theoretically, this absence may reflect under-reporting bias. Adequate blinding is virtually impossible with psychological therapy, and this is a major methodological problem with all studies in this area. Whether there is a specific biological mechanism by which psychological therapy may work in IBS has not been shown. Any benefit may derive from an empathic attitude of the health provider, reduction of life stresses because of attention from or discussion with the health provider, transference of enthusiasm by the provider about the potential effectiveness of therapy, and the quality and quantity of contact time with the provider.

Section 2.17 Effectiveness of herbal therapies and acupuncture in the management of irritable bowel syndrome

A systematic review of herbal therapy in IBS has been published (294). The Task Force reviewed the available RCTs when evaluating the evidence for benefit in this report (295–298). These trials mostly tested unique Chinese herbal mixtures, and they appeared to show a benefit (296–298). It is not possible to combine these studies into a meaningful meta-analysis, however, and overall, any benefit of Chinese herbal therapy in IBS

continues to be potentially confounded by the variable components used and their purity. Publication bias may also explain the lack of more negative trials. Furthermore, concerns about toxicity, especially liver failure, and also other serious side effects remain regarding use of any Chinese herbal mixture. A Cochrane systematic review (299) of acupuncture identified six poor quality trials that compared acupuncture with sham acupuncture. The outcomes assessed were heterogeneous and the review reported that the efficacy of this intervention is uncertain. Further work is needed before any recommendations on acupuncture or herbal therapy can be made.

Section 2.18 Emerging therapies for the irritable bowel syndrome

Our expanding knowledge of the pathogenesis of IBS has led to the identification of a wide variety of novel agents, now in various stages of development. This discussion will focus on drugs that have progressed beyond the proof of concept stage of development and will consider agents with predominantly peripheral effects, as well as those with both peripheral and central effects.

To prepare for this discussion, it is helpful to understand the steps involved in the FDA's drug development process (300). Preclinical development consists of animal studies, which address questions involving mechanism of action and drug toxicity. After submission of an Investigational New Drug Application to the FDA, clinical development can commence and consists of phases 1, 2, and 3 trials. Phase 1 trials typically are conducted in small numbers of healthy volunteers and evaluate drug toxicity and pharmacokinetics, i.e., the absorption, distribution, metabolism, and excretion of the drug being studied. Phase 2a trials evaluate the drug's pharmacodynamics, i.e., biochemical and physiologic effects, mechanisms of action, and the relationship between drug concentration and effects of the drug in healthy volunteers or patients. Phase 2b trials are randomized, placebo-controlled trials that involve larger numbers of patients and typically evaluate the efficacy and safety of a range of drug doses. Ideally, phase 2b study results inform the selection of the drug dose offering the best combination of efficacy and safety for phase 3 trials. Phase 3 trials are large, randomized, controlled registration trials that assess the efficacy and safety of the investigational drug vs. placebo in patients with the disease of interest. Typically, positive results from two phase 3 trials are necessary for drug approval. The specifics of the phase 3 trials regarding patient population, study methodology, and main study results determine the eventual product label contents should a drug gain FDA approval.

Agents with predominantly peripheral effects

Drugs which affect chloride secretion. Multiple types of chloride channels are present in nearly all cells, and are responsible for many cellular functions including modulation of cellular volume and fluid transport. CFTR, which is located on the apical membrane of intestinal cells, plays a major role in chloride ion transport and fluid secretion. Crofelemer is an extract from the *Croton lechleri* tree in South America that inhibits CFTR and also has anti-inflammatory and analgesic properties, making it an attractive agent for the treatment of IBS-D. A 12-week randomized, double-blind, placebo-controlled, phase 2 dose-ranging study involving 246 adults with IBS-D demonstrated safety and significant improvement in pain as well as trends toward improvement in urgency, stool frequency, and adequate relief of overall symptoms (301). A phase 2b trial assessing crofelemer's safety and efficacy in adult women with IBS-D is underway.

Guanylate cyclase-C is another intestinal transmembrane receptor responsible for chloride, bicarbonate, and fluid secretion into the intestinal lumen via production of cyclic guanosine monophosphate and consequent activation of CFTR (302). Linaclotide is a guanylate cyclase C agonist being developed as a treatment for IBS-C and chronic constipation. Linaclotide has been reported to increase colonic transit, improve stool consistency, stool frequency, and ease of stool passage in a randomized, double-blind, placebo-controlled trial of 36 women with IBS-C (303). Preliminary data from a recently completed phase 2b study, which randomized 420 patients with IBS-C to placebo, 75, 150, 300, and 600 μg of linaclotide daily for 12 weeks demonstrated benefits for stool frequency as well as global and other individual IBS-C symptoms. Phase III studies are expected to begin in the near future (304).

Calcium channel blockers. Arverapamil (AGI-003) is the r-isomer of the calcium channel blocker verapamil and is reported to selectively inhibit intestinal calcium channels. Averapamil recently demonstrated efficacy compared with placebo in a study of 129 adults with IBS-D (305). Phase 3 trials in adults with IBS-D are expected to begin in 2008.

Opioid receptor ligands. κ-Opioid agonists and μ-opioid antagonists are capable of modulating visceral sensation through effects on peripheral visceral afferent nerves. Compared with placebo, asimadoline, a peripheral κ-opioid agonist, decreased pain perception from colonic distention in female IBS patients (306). In a phase 2b dose-ranging study in 596 patients, asimadoline (0.15 mg, 0.5 mg, or 1.0 mg twice daily) was shown to improve pain, urgency, stool frequency, and bloating in patients with IBS-D and, to a lesser extent, patients with IBS-M. No benefits were observed in patients with IBS-C (307).

The peripheral μ-opioid antagonist, methylnaltrexone, has proven effective for inducing "laxation" (passage of a bowel movement) in terminally ill patients taking opioids and recently has been FDA approved for the treatment of opioid-induced constipation (308). This drug is typically administered every other day to daily as a subcutaneous injection. The role of this drug in the treatment of IBS-C remains to be established.

Motilin receptor ligands. Mitemcinal is a motilin receptor agonist that has demonstrated prokinetic properties in the lower gastrointestinal tracts of several animal models (309,310). A phase 2 clinical trial assessing mitemcinal's safety and efficacy in IBS is expected in the near future.

Agents with peripheral and central effects

Emerging serotonergic agents. Several serotonergic agents are in development for IBS. A recent randomized, placebo-controlled study found the 5-HT4 receptor agonist prucalopride to be more effective at increasing stool frequency than placebo in patients with chronic constipation (311). Studies evaluating the efficacy of prucalopride in patients with IBS-C are anticipated.

Ramosetron, a 5-HT_3 antagonist, currently is being evaluated as a treatment for patients with IBS-D. In a 12-week randomized, double-blind, placebo-controlled phase 3 trial of 539 patients from Japan, ramosetron was significantly more likely than placebo to achieve the primary endpoint of relief of global IBS symptoms (312); there were no serious drug-associated adverse events reported during this study. A new drug application for ramosetron treatment of IBS-D has been filed in Japan. In a 12-week phase 2 trial, which enrolled 691 IBS-D patients from Europe, all four ramosetron groups (2.5, 5, 10, 20 μg once daily) had a numerically higher responder rate for relief of global IBS symptoms and abdominal pain compared with placebo (312). Ischemic colitis has not been reported with ramosetron, though a relatively small number of patients have thus far been exposed to this drug. There are plans for phase 3 trials of this drug in the United States and Europe.

Several novel 5-HT receptor agents in early stages of clinical development may have future applications in the treatment of IBS-C. TD-5108 is a highly selective full 5-HT_4 agonist associated with increased stool frequency and decreased stool consistency in preclinical trials. A recent four-week multi-center, randomized, double-blinded, placebo-controlled phase 2 trial involving 400 patients with chronic constipation demonstrated TD-5108's safety, tolerability, and superiority over placebo in increasing weekly spontaneous bowel movements (313). In a recent press release by the manufacturer, three different daily doses of TD-5108 (15 mg, 30 mg, and 50 mg) each were superior to placebo in achieving the primary endpoint of increased spontaneous bowel movements and in key secondary endpoints including time to first spontaneous bowel movement and percentage of patients achieving a spontaneous bowel movement in the initial 24 h. This drug is also being considered as a potential treatment for patients with IBS-C.

The 5-HT_3 agonist DDP-733 demonstrated a statistically significant benefit for the subjective global assessment of IBS compared with placebo (54 vs. 15%) in a phase 2a trial in IBS-C patients (314). A randomized, blinded, placebo-controlled study is underway at multiple centers in Canada to assess the safety and efficacy of this drug in IBS-C.

Table 4. Emerging therapies for IBS

Agent	Mechanism of action	Targeted disorder	Clinical status
Peripheral acting agents			
Crofelemer (301)	CFTR inhibitor	IBS-D	Phase 2b complete
Linaclotide (MD-1100) (303)	Guanylate cyclase-c agonist	IBS-C	Phase 3
Arverapamil (AGI-003) (305)	Calcium channel blocker	IBS-D	Phase 3
Asimadoline (306)	Kappa opioid agonist	IBS	Phase 2b complete
Mitemcinal (326)	Motilin receptor agonist	IBS-C	Phase 2
Peripheral and central acting agents			
Ramosetron (312)	5-HT_3 antagonist	IBS-D	Phase 3
TD-5108 (313)	5-HT_4 agonist	IBS-C	Phase 2
DDP-773 (314)	5-HT_3 agonist	IBS-C	Phase 2
DDP-225 (315)	5-HT_3 antagonist and NE reuptake inhibition	IBS-D	Phase 2
BMS-562086 (318)	Corticotropin-releasing hormone antagonist	IBS-D	Phase 2
GW876008 (319)	Corticotropin-releasing hormone antagonist	IBS	Phase 2
GTP-010 (327)	Glucagon-like peptide	IBS pain	Phase 2
AGN-203818 (322)	Alpha receptor agonist	IBS pain	Phase 2
Solabegron (323)	Beta-3 receptor agonist	IBS	Phase 2
Espindolol (AGI-011) (324)	Beta receptor antagonist	IBS (all subtypes)	Phase 2
Dextofisopam (325)	2,3 benzodiazepinereceptors	IBS-D and IBS-M	Phase 3

IBS-C, irritable bowel syndrome with constipation; IBS-D, irritable bowel syndrome with diarrhea, IBS-M, mixed irritable bowel syndrome; CFTR, cystic fibrosis transmembrane conductance regulator.

DDP-225 is a novel partial 5-HT_3 antagonist and norepinephrine reuptake inhibitor. Preclinical studies with DDP-225 have reported decreases in GI motility and visceral hypersensitivity (315). A phase 2 clinical trial in patients with IBS-D is currently underway in Canada.

Corticotropin-releasing hormone antagonists. Corticotropin-releasing hormone (CRH) is one of the primary mediators of the hypothalamic pituitary adrenal axis. Exogenous CRH led to exaggerated colonic motility and associated abdominal discomfort in IBS patients compared with controls (316). A nonselective CRH antagonist reduced the anxiety, sensation, and motility evoked by electrical stimulation of the colon in a small cohort of IBS patients (317). A multi-center, randomized, placebo-controlled phase 2 trial of the CRH antagonist, BMS-562086 was recently completed in a group of women with IBS-D; results from this trial have not yet been announced (318). Another CRH antagonist, GW876008, is currently being evaluated in a multi-center, randomized, placebo-controlled phase 2 trial in IBS patients (319).

Autonomic modulators. There is growing evidence that specific forms of autonomic dysfunction can be identified in different subgroups of IBS patients (320,321). These discoveries have generated interest in evaluating autonomic receptor ligands as potential treatments for IBS.

AGN-203818, an α_2-receptor agonist, currently is being evaluated as a treatment for abdominal pain in a phase 2 clinical trial in patients with IBS (322). Solabegron is a β_3-adrenergic receptor agonist being evaluated as a treatment for the global symptoms of IBS in a multinational phase 2 clinical trial involving sites in Europe and Australia (323). The β-adrenergic receptor antagonist, espindolol (AGI-001), recently has been evaluated as a treatment for IBS in a randomized, double-blind, placebo-controlled trial employing a forced dose escalation protocol (324) Preliminary data did not demonstrate a difference in efficacy compared with placebo when all doses were taken into account, however, there was a trend toward significant improvement at the highest dose compared with placebo.

Dextofisopam is a nonsedating homophthalazine compound that is structurally distinct from traditional benzodiazepines and binds to 2,3 benzodiazepine receptors concentrated in the subcortical and hypothalamic regions of the brain. Such receptors are known to have modulatory effects on autonomic function and consequently, gastrointestinal motility and sensation. In a double-blind, placebo-controlled trial involving 140 patients (66 IBS and 74 placebo) with IBS-D and IBS-M, dextofisopam was well tolerated and proved superior to placebo in providing adequate relief of overall IBS symptoms as well as reducing stool frequency and improving stool consistency (325). An 18-month phase 2b trial is currently underway to further assess the efficacy of this drug in 480 women with IBS-D and IBS-M.

A summary of emerging therapies is given in **Table 4**.

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