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Irritable Bowel Syndrome

Irritable bowel syndrome (IBS) is a common gastrointestinal disorder, with a prevalence of 4% to 10%. It is a chronic condition characterized by abdominal pain in conjunction with altered bowel habits, abdominal distention, or bloating. IBS can present with 3 different defecation patterns: IBS with constipation, IBS with diarrhea, or mixed IBS. Recent advances in IBS include a positive diagnosis based on symptom-based criteria and a treatment plan based on IBS subtype and bothersome symptoms. In addition to diet and lifestyle modifications, this article discusses the role of new pharmacologic and nonpharmacologic treatment options for the management of IBS.

Diagnosis

Treatment

Practice Improvement

CME/MOC activity available at Annals.org.

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Irritable bowel syndrome (IBS) is a heterogeneous group of chronic bowel disorders characterized by altered stool frequency and form combined with abdominal pain or discomfort. Although IBS is recognized worldwide, the estimated prevalence varies significantly among countries (1–3). In the United States, the estimated prevalence is 4% to 10% depending on the diagnostic criteria or method used to assess prevalence (1, 3). IBS is more common in women and adults younger than 50 years and is frequently associated with psychosocial disturbances. The pathophysiology of IBS is complex and incompletely understood; potential mechanisms include genetic factors, immune system alterations, changes in gut microbiota, alterations in bowel motility, visceral hypersensitivity, increased activity in brain regions associated with pain processing and emotional regulation, and psychosocial comorbidities (4). Disruptions in intestinal environment, including changes in fecal levels of unconjugated bile acids, and dyssynergic defecation are now increasingly recognized as factors contributing to abnormal bowel function in this disease. IBS has therefore been redefined as a disorder of gut–brain interaction (5). Symptom severity is determined by the person's experience rather than by an objective test or biomarker, and symptoms may range from mild to debilitating. Greater severity of IBS symptoms has been associated with increased psychological and extraintestinal symptoms, more health care utilization, and poorer health-related quality of life. Three defecation patterns are characteristic of IBS: constipation-predominant (IBS-C), diarrhea-predominant (IBS-D), and mixed (alternating diarrhea and constipation) (IBS-M). Recognizing the predominant pattern and severity of IBS symptoms can help inform diagnostic and treatment decisions.

Diagnosis

What symptoms should prompt a clinician to consider IBS?

History is the primary tool for diagnosing IBS. Clinicians should suspect a diagnosis of IBS if a patient presents with abdominal discomfort or pain associated with abnormal stool frequency, with symptoms that wax and wane and that may be exacerbated by psychosocial stress. Other symptoms suggestive of IBS include abdominal bloating or distention, flatulence, urgency, excessive straining, or incomplete evacuation. The presence of conditions such as chronic fatigue, fibromyalgia, interstitial cystitis, sleep disturbance, and psychiatric comorbidity also favors an IBS diagnosis.

Because individual symptoms may vary and have poor sensitivity and specificity to diagnose IBS, diagnostic criteria incorporating a combination of symptoms have been developed. In 1978, Manning and colleagues (6) proposed the first IBS criteria based on symptoms. Building on this, another set of consensus-based criteria, known as the Rome criteria, was developed by a group of experts in 1989. The current version, released in 2016, is the Rome IV criteria, which are widely accepted and used as the standard diagnostic criteria for IBS (7). Rather than viewing IBS as a "diagnosis of exclusion," a positive diagnosis of IBS can be reliably made using the following clinical criteria: recurrent abdominal pain at least 1 day a week on average for 3 months, plus at least 2 of the following: defecation-related pain, change in stool frequency, or change in stool consistency (with symptom onset ≥6 months before diagnosis) (7) (see the **Box**: Symptom Criteria for IBS). The sensitivity and specificity of the Rome IV criteria in diagnosing IBS are 62.7% and 97.1%, respectively (8). When diagnostic criteria are satisfied, alarm features are absent, and the history and physical examination suggest IBS, the risk for overlooking organic disease may be as low as 1% to 3% (8).

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Symptom Criteria for IBS

Rome IV criteria*

Recurrent abdominal pain on ≥1 d/wk on average in the previous 3 months, related to ≥2 of the following:

- Defecation
- Change in stool frequency
- Change in stool form (appearance)

** Criteria should be fulfilled over the previous 3 months, with symptom onset ≥6 months before diagnosis.*

In patients with high suspicion for a diagnosis of IBS based on history, further evaluation can be facilitated by understanding the pattern of symptoms and placing the patient into one of the following subtypes: IBS-C, IBS-D, IBS-M, or IBS unclassified. Furthermore, the Bristol Stool Form Scale can be a helpful tool for assessing stool consistency, understanding symptoms, and tracking progress in people with IBS (7) (see the Box: Bristol Stool Form Scale).

What other conditions should be considered during evaluation of a patient with possible IBS?

The differential diagnosis of IBS is extensive (Table 1). Clinicians should consider symptom patterns when trying to exclude other serious diagnoses that can masquerade as IBS. In patients with decreased stool frequency, incomplete evacuation, and abdominal pain, clinicians should consider a diagnosis of partial colonic obstruction or nonobstructive colonic dysmotility disorders secondary to medications, neurologic disease, hypothyroidism, pelvic floor dysfunction, or colonic inertia (colon transit >5 days). The differential diagnosis in patients with diarrhea includes inflammatory bowel disease, infection, carbohydrate and bile acid malabsorption, effects of medication, and diet. Excessive consumption of lactose, fructose, and caffeine may result in loose stools in susceptible patients. *Clostridioides difficile* infection should be excluded in patients who have recently received antibiotics. Inquiring about travel to regions where endemic infections, such as giardiasis, are prevalent may also guide further testing. In addition, studies have shown considerable symptom overlap between IBS-D and microscopic colitis (9).

What is the utility of the physical examination?

A physical examination should be part of the evaluation to reassure patients and to help exclude other causes of the symptoms. Most patients with IBS have no abnormal findings on physical examination. In some cases, patients may have some mild abdominal tenderness or distention on palpation of the abdomen, which is a nonspecific finding. Most experts recommend performing a digital rectal examination to evaluate for possible dyssynergic defecation and a rectal mass, especially in patients

Bristol Stool Form Scale

The Bristol Stool Form Scale may be used to differentiate stool types by appearance:

- Type 1 = Separate hard lumps, like nuts
- Type 2 = Sausage-shaped but lumpy
- Type 3 = Like a sausage but with cracks on its surface
- Type 4 = Like a sausage or snake but smooth and soft
- Type 5 = Soft blobs with clear cut edges
- Type 6 = Fluffy pieces with ragged edges; a mushy stool
- Type 7 = Watery; no solid pieces

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Table 1. **Differential Diagnosis of IBS**

Disease	*Clinical Characteristics*	*Possible Diagnostic Strategies*
Constipation-predominant symptoms		
Strictures due to inflammatory bowel disease, diverticulitis, ischemia, or cancer	Obstipation, constipation	CT scan, CT or magnetic resonance enterography, colonoscopy, flexible sigmoidoscopy, barium enema
Colonic inertia	Very infrequent bowel movements	Radiopaque markers, scintigraphy
Pelvic floor dysfunction*	Straining, self-digitation	Rectal examination, anorectal manometry with balloon expulsion test, MRI defecography
Neurologic disease*	Concurrent Parkinson disease, autonomic dysfunction (Shy–Drager), multiple sclerosis	History and neurologic examination
Medication*	Opiates, cholestyramine, calcium-channel blockers, anticholinergic medications	Medication history
Hypothyroidism*	Other signs and symptoms of hypothyroidism	Serum thyroid-stimulating hormone
Diarrhea-predominant symptoms		
Crohn disease	Diarrhea, abdominal pain	Colonoscopy, CT or magnetic resonance enterography, small-bowel barium radiograph
Ulcerative colitis	Likely to have rectal bleeding in addition to diarrhea, abdominal pain, tenesmus	Colonoscopy
Microscopic colitis	Watery diarrhea, often with nocturnal symptoms	Colonoscopy/flexible sigmoidoscopy and biopsy
Infectious	Abdominal discomfort, diarrhea (especially in the setting of recent travel)	Ova and parasites ×3, stool culture, stool *Giardia* antigen, metronidazole trial
Clostridioides difficile infection	Recent antibiotic treatment	Stool polymerase chain reaction
Small intestinal bacterial overgrowth	Diarrhea, bloating, abdominal distention	Jejunal aspirate, hydrogen breath test, antibiotic trial
Celiac disease	Diarrhea, usually steatorrhea, anemia	Tissue transglutaminase antibody, endoscopy with small-bowel biopsy
Lactose intolerance	Symptoms worsen with lactose consumption	Avoidance trial, lactose breath test
Hyperthyroidism	Loose stools and other features of hyperthyroidism	Serum thyroid-stimulating hormone
Neuroendocrine tumor	Carcinoid, gastrinoma, VIP-producing tumor	Urine 5HIAA, fasting gastrin (followed by secretin stimulation test), serum VIP, PET dotatate scan
Pain-predominant symptoms		
Aerophagia, bloating	Patient may be anxious (nervous air swallowing), can be exacerbated by antireflux surgery	Abdominal radiograph, pH-impedance study
Intermittent small-bowel obstruction	More likely with history of abdominal surgeries	Abdominal radiograph, CT scan, small-bowel barium radiograph
Acute intermittent porphyria	Rare; may have elevated liver enzymes and neurologic symptoms	Serum and urine porphyrins, especially porphobilinogen, and δ-aminolevulinic acid
Ischemia	Intestinal angina, especially in patients with atherosclerosis; food aversion; weight loss; pain 15–40 min after meals	CT angiography, Doppler ultrasonography, mesenteric angiography
Chronic pancreatitis	Epigastric pain, usually more persistent than with usual IBS	Abdominal radiograph to assess for calcifications, CT scan, endoscopic ultrasonography
Lymphoma of gastrointestinal tract	Weight loss (typically)	CT scan, small-bowel radiograph, endoscopy with biopsies
Endometriosis	Menstrual-associated symptoms, pelvic symptoms	Laparoscopy

5HIAA = 5-hydroxyindoleacetic acid; CT = computed tomography; IBS = irritable bowel syndrome; MRI = magnetic resonance imaging; PET = positron emission tomography; VIP = vasoactive intestinal peptide.
** Unlikely to cause abdominal pain by itself.*

with constipation. In dyssynergic defecation, there is paradoxical contraction of the anal sphincter on bearing down and reduced perineal descent; patients with such findings would benefit from anorectal manometry (10) and referral for pelvic floor therapy.

When should clinicians consider consultation with a gastroenterologist?

Most patients initially consult their primary health care professional for evaluation of symptoms. In many cases, gastrointestinal (GI) specialty care is needed to exclude diseases that can mimic IBS symptoms. Consultation is warranted when patients do not respond to initial management; when they have alarm symptoms and may need diagnostic procedures, such as endoscopy; or when they have severe symptoms, especially pain.

Which diagnostic tests are useful?

Health care professionals are often concerned about missing a GI condition, such as inflammatory bowel disease, celiac disease, or cancer, that explains the IBS symptoms, leading to a work-up and evaluation that includes invasive testing. However, routine use of diagnostic tests is not recommended in the absence of alarm symptoms. In addition, continually performing screening tests may increase the belief that something is being missed, and patients are often dissatisfied with negative findings on repeated or multiple tests (with no improvement in quality of life) (11). Therefore, multiple guidelines recommend limited diagnostic testing in patients with IBS symptoms as discussed earlier (12–14).

Certain clinical features, often called alarm features or red flag signs, warrant further diagnostic testing or evaluation (see the Box: Alarm Features That Suggest Possible Organic Disease). Alarm features include onset of symptoms after age 50 years; rectal bleeding or blood in the stool; unintentional weight loss; iron deficiency anemia; nocturnal awakening due to GI symptoms; fever in association with bowel symptoms; and symptoms in a person with a family history of colorectal cancer, inflammatory bowel disease, or celiac disease.

Laboratory and stool studies

It is reasonable to obtain a complete blood count, a complete metabolic panel, and C-reactive protein level, as these tests are inexpensive and can reassure the clinician and the patient (11). If the clinical suspicion for thyroid disease is high, a thyroid profile should be obtained. A serologic test for celiac disease (measuring levels of tissue transglutaminase antibody) may be useful in patients with possible IBS-D; data show that the prevalence of celiac disease in patients with IBS is between 0.7% and 3%, and the odds of having celiac disease are 2-fold higher compared with

Alarm Features That Suggest Possible Organic Disease

- Symptoms
  - Unintentional weight loss
  - Nocturnal awakening due to GI symptoms
  - Fever in association with bowel symptoms
  - Rectal bleeding or blood in stool
  - Iron deficiency anemia
- History
  - New-onset, progressive symptoms
  - Onset of symptoms after age 50 years
  - Recent antibiotic use
  - Family history of colorectal cancer, inflammatory bowel disease, or celiac disease
- Physical findings
  - Abdominal mass
  - Enlarged lymph nodes

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the general population (15, 16). *C difficile* infection should be excluded in patients with IBS-D who have recently received antibiotics. Examination of stool for ova and parasites may also be helpful in patients with suspected IBS-D, especially if a travel history suggests potential exposure to parasites. In general, bacterial cultures are unlikely to be helpful. Breath testing in this population can be misleading, as false-positive results are common and the results may reflect altered orocecal transit times rather than actual bacterial overgrowth. Measurement of fecal calprotectin in stool samples can help identify patients with intestinal inflammation and is most useful in patients in whom inflammatory bowel disease is clinically suspected. A fecal calprotectin level less than 40 mcg/g is associated with a less than 1% chance of having inflammatory bowel disease (17). In patients with prior cholecystectomy, testing for bile acid diarrhea (BAD) may be considered.

Endoscopy and imaging studies

Invasive tests such as upper endoscopy or colonoscopy should be considered when alarm features are elicited or the history or laboratory studies raise concern about an underlying inflammatory condition. In patients with suspected IBS-D, colonoscopy with random biopsies to rule out microscopic colitis should be performed, especially in patients who have symptoms despite adequate initial therapy or in middle-aged or older patients with new-onset diarrhea and severe symptoms. Colonoscopy should also be considered if patients are due for colorectal cancer screening or surveillance according to guidelines for the general population. In the absence of alarm features, imaging studies have limited value. A flat and upright abdominal radiograph or cross-sectional imaging should be considered on a case-by-case basis, particularly in patients suspected of having an evacuation disorder.

BAD is an important differential diagnosis in patients who present with frequent loose stools or diarrhea. Diagnostic testing using selenium-75-homocholic acid taurine is currently unavailable in the United States. In clinical practice, a therapeutic trial with a bile acid–binding agent is often used as an indirect assessment of BAD. However, the introduction of a combined test consisting of serum 7αC4 and fecal concentration of total bile acids or percentage of primary bile acids, which is offered by reference laboratories in many countries (including the United States), provides the opportunity to make a positive diagnosis of BAD (18, 19). Carbohydrate malabsorption is another differential diagnosis in patients with diarrhea symptoms. Lactose or fructose hydrogen breath tests can be considered for diagnostic testing, but a trial period of dietary exclusion of the suspected carbohydrate for several weeks is often used instead.

Finally, *Giardia* testing should be performed in areas where it is endemic. If celiac disease is suspected based on a positive serologic test result or clinical or family history, an upper GI endoscopy with duodenal biopsies should be performed. Small intestinal bacterial overgrowth has been proposed to be common in IBS, but its prevalence and clinical importance are uncertain; therefore, routine clinical testing for this should not be done.

Role of biomarkers

Current evidence and expert consensus do not support application of biomarkers in routine clinical care of IBS (12). However, the promise of a future valid biomarker in IBS could serve many purposes, such as to facilitate diagnosis, distinguish IBS from organic illness, predict prognosis, discriminate among various IBS subtypes to guide individualized treatment, improve drug development, and monitor therapeutic efficacy (20). Examples of such biomarkers could allow for accurate measurement of colonic transit, a positive diagnosis of evacuation disorders, or BAD.

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Diagnosis... Clinicians should base the diagnosis of IBS on the history and physical examination, paying careful attention to fulfillment of the Rome criteria and exclusion of alarm features. Patients who meet the criteria and have no alarm features may not need additional testing. Any proposed diagnostic testing should be judicious and should focus on excluding specific non-IBS conditions that are consistent with the clinical presentation of each patient.

CLINICAL BOTTOM LINE

Treatment

Management of IBS requires a multidisciplinary integrated approach, including establishment of an effective patient–clinician relationship, education, and reassurance combined with lifestyle, dietary, pharmacologic, behavioral, and psychological treatment. Although many patients with mild IBS respond to lifestyle and dietary modifications, those with ongoing symptoms require additional pharmacologic and behavioral therapies depending on the predominant symptoms and their severity.

Are dietary modifications or restrictive diets effective in the management of IBS?

Many patients with IBS associate their GI symptoms with eating food. Dietary modification is reasonable for persons who report meal-related symptoms and need to improve their diet quality. The patient should receive general counseling about avoidance of foods that can exacerbate symptoms, such as excess fats (which can lead to gas retention), nondigestible carbohydrates (which can lead to fermentation and gas formation), excess caffeine, and carbonated drinks (21). If professional dietary counseling is accessible (and covered), education by a registered dietitian or nutritionist can benefit motivated patients who are unable to implement dietary recommendations independently. Diet modifications should be followed for a predetermined period, typically 4 to 6 weeks, and abandoned if there is insufficient clinical response. Disordered eating is common in patients with GI disorders. Patients who report excessively restrictive dietary patterns should be screened for disordered eating and, if appropriate, referred to eating disorder and/or mental health specialists.

Gluten-free diets (GFDs) are popular among patients with IBS and the population at large, and many people report having completed a trial of gluten-free foods to help with symptoms. However, the rationale for gluten exclusion in IBS has yet to be established, and a GFD is not uniformly recommended in patients with IBS (22).

There is insufficient evidence to recommend a GFD to improve symptom control in patients with IBS. Two placebo-controlled rechallenge trials have shown improved symptom control while patients consumed a GFD, yet meta-analysis of these trials showed that the benefit of gluten restriction on overall symptom control was extremely variable (relative risk [RR], 0.42 [95% CI, 0.11 to 1.55]) (22).

A low-FODMAP (fermentable oligosaccharides, disaccharides, monosaccharides, and polyols) diet can improve symptoms and quality of life in patients with IBS-D (21). Patients advised to follow a low-FODMAP diet should start with an initial strict restrictive phase lasting 4 to 6 weeks. Only those who show clinical benefit should advance to the 6- to 10-week reintroduction phase, when they are challenged with foods containing a single FODMAP while carefully monitoring symptoms. People

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with eating disorders should avoid restrictive diets. A long-term low-FODMAP diet should be personalized based on symptom data collected during the reintroduction phase.

A recent randomized controlled trial (RCT) that followed the paradigm of FODMAP diet personalization showed a significantly higher response in the low-FODMAP group than the traditional dietary advice group (52.9% vs. 30.6%; P = 0.03). A strict short-term low-FODMAP diet and a long-term modified low-FODMAP diet led to overall improvement in IBS-D symptoms and quality of life (23).

A recent network meta-analysis of 13 RCTs with 944 patients showed that a low-FODMAP diet ranked first over a habitual diet in improving global IBS symptoms. A low-FODMAP diet was superior to National Institute for Health and Care Excellence dietary advice for abdominal bloating or distention (RR, 0.72 [CI, 0.55 to 0.94]) (24).

Inadequate fiber consumption may contribute to constipation in patients with IBS-C. Soluble fibers, such as oats and psyllium (ispaghula) or polycarbophil compounds (for example, Citrucel or FiberCon), are preferred over insoluble fibers, such as wheat bran or brown rice. Insoluble fiber does not significantly improve global symptoms in IBS and may exacerbate abdominal pain and increase bloating. The overall safety profile of soluble fiber and its positive effect on stool viscosity and fermentation favor its use despite small documented clinical benefit in patients with IBS-C.

A meta-analysis of 14 RCTs with 906 patients with IBS found a small benefit of soluble fiber (RR, 0.83 [CI, 0.73 to 0.94]), with a number needed to treat (NNT) of 10 (25). A more recent network meta-analysis of 5 trials utilizing fiber did not show significant benefit over placebo in providing symptom control, possibly related to the overall short duration of the included studies, their low quality, and exclusion of a positive ispaghula husk study from the analysis (26).

Are nonpharmacologic interventions, such as lifestyle modifications or acupuncture, useful in management of IBS?

Nonpharmacologic interventions for reducing IBS symptoms include lifestyle adjustments, such as incorporation of mild exercise or physical activity. Although the data have limitations, studies suggest that various forms of exercise can improve global symptoms and possibly improve quality of life or anxiety but have no effect on abdominal pain.

A meta-analysis of various forms of exercise (such as yoga, walking, cycling, swimming, and running) reported a positive effect on GI symptoms, quality of life, and anxiety in patients with IBS (n = 683); however, there was heterogeneity among studies (27). In another systematic review, 6 RCTs (n = 185) were pooled to explore the benefit of physical activity on IBS symptoms. The data suggested that physical activity may improve IBS symptoms but may not have an effect on overall quality of life or abdominal pain (low-certainty evidence) (28).

Acupuncture has been the subject of many studies, but its benefits remain uncertain. Acupuncture is generally well tolerated and received by patients expressing preference for complementary interventions. Reported adverse effects are minor and include skin and nerve irritation, possible infections, minor bleeding, or exacerbation of symptoms. In one study that compared true acupuncture with sham acupuncture, IBS symptom improvement was seen in both groups (53% for true acupuncture and 42% for sham acupuncture), suggesting that acupuncture does not have a specific treatment effect in IBS and may reflect a placebo response (29). Future studies on use of acupuncture in IBS are needed to clarify whether treatment benefit is related to patient preferences and expectations across various populations

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or whether the intervention is associated with a true-positive effect.

A meta-analysis of 16 RCTs (n = 1305) showed that acupuncture has a beneficial effect on symptom severity in patients with IBS-D and comorbid anxiety and depression (30).

What is the role of behavioral therapy or psychotherapy in the management of IBS?

The overlap of psychological disorders with IBS has led to the investigation of several behavioral therapies to help reduce IBS symptoms. The 4 major psychologically based therapies for patients with IBS are cognitive behavioral therapy (CBT), psychodynamic (interpersonal) therapy, hypnotherapy (gut-directed hypnosis), and mindfulness-based therapy.

Although the evidence is mixed regarding long-term improvement in GI symptoms with successful treatment of psychiatric comorbidities and behavioral therapies, data show that CBT, psychotherapy, and hypnotherapy are more effective than usual care in relieving global symptoms of IBS (low-quality evidence) (31). The best available evidence is for CBT, which teaches patients techniques for changing their behavior and thought processes about their condition. CBT has been shown to improve quality of life and reduce symptom severity in patients with IBS, especially pain perception and comorbid depressive and anxiety disorders. The NNTs are 3 for CBT, 3 for multicomponent psychological therapy, and 2 for hypnotherapy; all approaches are more effective than sham therapy or usual care for IBS (31, 32). A 2024 systematic review and network meta-analysis showed that several brain–gut behavioral treatments, including self-guided or minimal-contact CBT, face-to-face multicomponent behavioral therapy, and face-to-face gut-directed hypnotherapy, might be efficacious for abdominal pain in IBS, although none was superior to another (33). Guidelines recommend adjunctive psychotherapy for patients whose symptoms do not respond to pharmacotherapy after 12 months or who have continued symptoms (34).

Which pharmacologic therapies are effective for management of IBS?

Current pharmacologic treatments (Table 2) are generally aimed at improving one or more of the predominant symptoms, such as abdominal pain, constipation, or diarrhea.

Therapies aimed at improving global symptoms, abdominal pain, or bloating

Antispasmodics are indicated on an as-needed basis as a first-line treatment to alleviate abdominal spasms and cramps associated with IBS. Although antispasmodic agents are pharmacologically diverse, they all reduce pain by reducing smooth-muscle contraction and may influence visceral hypersensitivity. Only 3 agents—dicyclomine, hyoscyamine, and peppermint oil—are available in the United States. Whether antispasmodics are more efficacious in specific IBS subtypes is unclear, but regular use in patients with constipation may be limited due to anticholinergic effects. Although these medications are often recommended for the treatment of postprandial IBS symptoms, use for this indication has not been specifically evaluated in clinical trials. The most common adverse events are dry mouth, dizziness, and blurred vision.

A meta-analysis of 22 RCTs (n = 1983) with 12 antispasmodics found that these agents led to clinically meaningful improvement in global symptoms and abdominal pain (risk ratio, 1.49 [CI, 1.25 to 1.77]; NNT, 5). However, the effect of individual agents was difficult to interpret given the small number of studies evaluating each drug (low-certainty evidence) (35).

Central neuromodulators work on 5-hydroxytryptamine, noradrenalin, and dopamine receptors along the brain–gut axis and are useful in treating psychiatric comorbidities, modifying gut motility, improving central downregulation of visceral signals, and enhancing neurogenesis in patients with IBS. The central neuromodulator for treatment of

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Table 2. **Medications Commonly Used to Treat IBS**

Class/Examples	*Mechanism of Action*	*Benefits*	*Adverse Events*
Treatments aimed at improving global symptoms, abdominal pain, or bloating			
Antispasmodics: Dicyclomine, hyoscyamine, peppermint oil	Reduces smooth-muscle contractions and may reduce visceral hypersensitivity	Useful for treatment of abdominal spasms and cramps associated with IBS Can be taken on an as-needed basis	Dry mouth, dizziness, blurred vision
Antidepressants: TCAs, SSRIs	May have analgesic properties in addition to mood-improving effects, but exact mechanism of action is unclear	TCAs are effective in improving global symptoms and abdominal pain SSRIs do not show positive effect on global IBS symptoms or abdominal pain	Dry mouth and drowsiness TCAs can reduce intestinal transit and exacerbate constipation
Antibiotic: Rifaximin	Alters gut microbiota	Given as a 2-wk course Shown to improve global IBS symptoms, particularly bloating	No adverse events
Treatments aimed at IBS-C			
Osmotic laxative: Polyethylene glycol	Causes water to be retained in the colon, leading to softer stools and increased stool frequency	Used as first-line treatment for IBS-C Effective in improving symptoms associated with constipation, including improved stool consistency, increased frequency, and decreased straining	Generally well tolerated May worsen bloating
Guanylate cyclase-C agonist: Linaclotide and plecanatide	Induces intestinal chloride and bicarbonate secretion via activation of the cystic fibrosis transmembrane conductance regulator, resulting in acceleration of intestinal transit May also have an analgesic effect	Effective as second-line treatment in patients with IBS-C Linaclotide shown to reduce abdominal pain and improve constipation, global symptoms, and health-related quality of life Plecanatide shown to improve global symptoms and stool frequency and reduce straining, bloating, and abdominal pain	Most common treatment-related adverse event leading to discontinuation was diarrhea
Lubiprostone	Activates type 2 chloride channel and increases chloride influx into the lumen of the gastrointestinal tract, resulting in accelerated intestinal transit	Shown to improve overall symptoms and reduce abdominal pain Approved for treatment of women with IBS-C	May cause nausea, bloating, and diarrhea
Tenapanor	Small-molecule inhibitor of the gastrointestinal sodium–hydrogen exchanger isoform 3 Decreases absorption of sodium and phosphate and increases water secretion into the intestinal lumen	Shown to relieve IBS symptoms, reduce abdominal pain, and increase number of complete spontaneous bowel movements	Well tolerated Most common adverse effects include diarrhea, bloating, and dizziness
Tegaserod	Partial agonist of the 5-HT4 receptor	Shown to improve overall IBS symptoms, reduce abdominal pain, and increase bowel movement frequency	Diarrhea and headaches were most frequent Risk for cardiovascular ischemic events Use limited to women aged <65 y
Treatments aimed at IBS-D			
Antidiarrheal: Loperamide	Inhibits peristalsis, leading to prolonged transit time and reduced stool frequency	Effective as first-line treatment in IBS-D or mixed IBS Shown to reduce stool frequency but has no effect on global IBS symptoms, abdominal pain, or bloating	Generally well tolerated

Continued on following page

Table 2–**Continued**

Class/Examples	*Mechanism of Action*	*Benefits*	*Adverse Events*
Selective 5-HT3–receptor antagonist: Alosetron	Decreases colonic motility and secretion	Approved for use in women who have had severe IBS-D for >6 mo and failure of conventional treatment Improves global symptoms, abdominal pain, and stool consistency	Ischemic colitis, severe constipation (leading to an alosetron prescribing program)
μ-Opioid receptor agonist and δ-opioid receptor antagonist: Eluxadoline	Leads to slower gastrointestinal transit and decreased visceral pain	Newer agent effective at improving abdominal pain and diarrhea	Nausea, constipation, abdominal pain, and pancreatitis

5-HT3 = 5-hydroxytryptamine receptor 3; 5-HT4 = 5-hydroxytryptamine receptor 4; IBS = irritable bowel syndrome; IBS-C = constipation-predominant irritable bowel syndrome; IBS-D = diarrhea-predominant irritable bowel syndrome; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant.

IBS should be chosen according to the pharmacologic properties and predominant symptoms. The first-line treatment for pain management in IBS is tricyclic antidepressants (TCAs). An alternative for pain management is serotonin–norepinephrine reuptake inhibitors. Selective serotonin reuptake inhibitors (SSRIs) are useful when symptoms of anxiety and hypervigilance are dominant or if there is coexisting depression, but they are not helpful for treating abdominal pain. It is also important to consider the predominant bowel habit when choosing a neuromodulator to treat IBS; SSRIs should be avoided in patients with diarrhea, and TCAs may cause constipation. These drugs are generally started at low doses and increased gradually (dosages vary depending on the agent prescribed). To ensure adherence, clinicians should educate patients about the mechanism of action of central neuromodulators and their slow onset of action, as a clinical response may not be seen for 6 to 8 weeks (36).

In a systematic review of 12 RCTs (n = 787) examining various TCAs in patients with IBS, the NNT to improve IBS symptoms was 4.5 (CI, 3.5 to 7) (37). The incidence of adverse events was significantly higher among those taking antidepressants compared with placebo (RR for any adverse event, 1.56 [CI, 1.23 to 1.98]; number needed to harm, 8.5). The ATLANTIS trial (38), conducted in primary care practices, confirmed that low-dose (titrated) amitriptyline was superior to placebo across multiple outcomes, was safe, and was well tolerated. Nevertheless, it is worth noting that the mean difference in IBS symptom severity scores between amitriptyline and placebo was modest and patients still experienced moderate symptoms at the end of the trial period.

Alterations in gut flora have been identified in patients with IBS, and small intestinal bacterial overgrowth may play a role in symptoms. Rifaximin is a poorly absorbed antibiotic that has been shown to improve global symptoms, abdominal pain, and bloating (39). Rifaximin dosing for this indication is 550 mg 3 times per day for 14 days. Its efficacy may diminish over time, necessitating repeated treatment.

Based on 3 RCTs (n = 1258), rifaximin was associated with improvement in abdominal pain (RR, 0.87 [CI, 0.80 to 0.95]) and bloating (RR, 0.86 [CI, 0.70 to 0.93]) as well as global relief of IBS-D symptoms (RR, 0.87 [CI, 0.80 to 0.94]) compared with placebo (39).

Probiotics may work through direct alteration of microbiota or indirectly via gut immune modulation, but their exact mechanism is unknown. Many trials involving different formulations have examined the effect of probiotics on global IBS symptoms and abdominal pain, with mixed results. At this time, it is not possible to reach any definitive conclusions about probiotic efficacy, the optimal formulation of organisms that should be administered, or dose and

duration of treatment or even to define populations who may be most likely to benefit from treatment (40).

Therapies for patients with IBS-C

In patients with IBS-C, osmotic laxatives, such as polyethylene glycol, can help increase the frequency of spontaneous bowel movements and improve constipation symptoms (41). Hypertonic osmotic laxatives, such as milk of magnesia, magnesium citrate, and sodium phosphate, draw water into the bowel and should be used with caution in older adults and those with renal impairment because of the risk for electrolyte abnormalities and dehydration. Lactulose, also an osmotic laxative, should be avoided in patients with IBS because it is broken down by colonic flora and produces excessive gas and is often not well tolerated. A limitation of osmotic laxatives is their lack of effect on other IBS symptoms, such as abdominal pain or discomfort.

Linaclotide and plecanatide are guanylate cyclase-C (GC-C) agonists, which are commonly used as second-line therapy after laxatives have failed in patients with moderate to severe symptoms. Mechanistically, they induce secretion of intestinal chloride and bicarbonate via activation of the cystic fibrosis transmembrane conductance regulator, resulting in acceleration of intestinal transit (42, 43). Linaclotide is approved for treatment of IBS-C at a dosage of 290 mcg once daily and is effective in reducing constipation symptoms as well as abdominal pain; the maximal effect on abdominal pain relief may take up to 12 weeks. Plecanatide is pH-sensitive and, compared with linaclotide, has a higher affinity for the GC-C receptor in the more acidic environment of the proximal duodenum. Plecanatide is U.S. Food and Drug Administration (FDA)–approved for treatment of IBS-C at a dose of 3 mg once daily. Diarrhea is an adverse effect of both medications, with no difference in odds of diarrhea between them (44).

A systematic review of 4 RCTs involving 2612 patients with IBS-C showed that linaclotide led to a clinically significant reduction in abdominal pain combined with less constipation (RR, 0.81 [CI, 0.77 to 0.85]). In addition, patients reported global symptom improvement and improved health-related quality of life (high-certainty evidence) (45). *Plecanatide was evaluated in 2 RCTs (n = 1632 patients with IBS-C) and was associated with clinically significant improvement in abdominal pain and constipation symptoms (RR, 0.87 [CI, 0.83 to 0.92]) compared with placebo (moderate-certainty evidence)* (45).

Lubiprostone, a direct-acting chloride-channel type 2 activator, increases chloride influx into the lumen of the GI tract, resulting in fluid secretion and accelerated intestinal transit (46). Lubiprostone is FDA-approved at a dose of 8 mcg twice daily for treatment of women with IBS-C. It is associated with clinically significant improvement in overall IBS symptoms and abdominal pain.

Across 2 RCTs involving 1154 patients, lubiprostone was associated with greater relief of symptoms and abdominal pain and improved constipation compared with placebo (RR, 0.88 [CI, 0.79 to 0.96]). The effect on improvement of spontaneous bowel movements was not significant (moderate-certainty evidence) (45).

Tenapanor is a small-molecule inhibitor of sodium–hydrogen exchanger isoform 3 (NHE3) in the GI tract. It decreases sodium and phosphate absorption and increases water secretion into the intestinal lumen. Tenapanor has been found to have antinociceptive effects. It is FDA-approved for treatment of IBS-C at a dose of 50 mg twice daily. The most common adverse effect is diarrhea.

Based on 3 RCTs (n = 1372), patients with IBS-C taking tenapanor demonstrated greater relief of IBS symptoms (RR, 0.71 [CI, 0.61 to 0.82]) and clinically significant improvement in abdominal pain and number of complete spontaneous bowel movements (RR, 0.84 [CI, 0.79 to 0.90]) compared with placebo (moderate-certainty evidence) (45).

Tegaserod is a partial agonist of the 5-hydroxytryptamine receptor 4 (5-HT4) that stimulates GI motility and increases fluid in the GI tract. Tegaserod was first approved by the FDA for short-term treatment of IBS-C in 2002. In 2007, it was withdrawn from the market because of concerns about the higher rate of cardiovascular ischemic events. After analysis of additional observational data, tegaserod was reapproved in 2019 at a dose of 6 mg twice daily with restrictions limiting use to women with IBS-C younger than 65 years with no history of myocardial infarction, stroke, transient ischemic attack, or angina.

Based on a systematic review of 4 RCTs (n = 1883), women with IBS-C treated with tegaserod demonstrated greater relief of overall IBS symptoms (RR, 0.85 [CI, 0.74 to 0.97]), abdominal pain, and improvement in bowel movement frequency (RR, 0.87 [CI, 0.81 to 0.93]) compared with placebo (moderate-certainty evidence). There was a small positive effect on quality of life, but it was not statistically or clinically significant (45). Similar outcomes were seen when the analysis was

limited to women without cardiovascular risks.

Therapies for patients with IBS-D

Loperamide, a nonabsorbable synthetic μ-opioid–receptor agonist, inhibits peristalsis, resulting in prolonged intestinal transit. Loperamide can be taken as needed or on a schedule depending on the severity and frequency of symptoms (4 mg orally initially and then 2 mg after each unformed stool, up to 16 mg/d). No safety concerns have been identified as being associated with repeated use of loperamide (47); however, data on efficacy in relieving GI symptoms, such as abdominal pain, are limited.

Two small double-blind RCTs (48, 49) have evaluated loperamide in patients with IBS and shown efficacy in reducing diarrhea (low-certainty evidence).

Alosetron, a selective 5-hydroxytryptamine receptor 3 (5-HT3) antagonist, reduces pain and diarrhea in patients with IBS-D by increasing colonic compliance and reducing intestinal transit. Alosetron was originally approved by the FDA in 2000 for treatment of IBS-D in women; however, it was voluntarily withdrawn from the market due to serious adverse events, namely ischemic colitis and serious complications of constipation. In 2002, the FDA approved reintroduction under a risk management program and restricted use to women with severe symptoms (frequent and severe abdominal pain or discomfort, frequent bowel urgency or fecal incontinence, and disability or restriction of daily activities due to IBS) who have not responded to conventional therapy. In a postmarketing safety study with 9 years of follow-up, the incidence of ischemic colitis was 1.03 cases per 1000 patient-years and the incidence of serious complications of constipation was 0.25 case per 1000 patient-years (50). Only 1 of 29 cases with significant comorbidities predisposing to ischemia required surgical management of ischemic colitis.

A systematic review of 8 RCTs that included 4227 patients demonstrated the beneficial effects of alosetron versus placebo in patients with IBS-D. Alosetron was superior to placebo in improving global symptoms (RR, 0.60 [CI, 0.54 to 0.67]) and IBS pain and discomfort (RR, 0.83 [CI, 0.79 to 0.88]). In addition, the individual studies showed that alosetron improved urgency, stool consistency, and score on the IBS-QOL questionnaire (moderate-certainty evidence) (39).

Eluxadoline is a μ-opioid–receptor agonist and δ-opioid–receptor antagonist that was approved in 2015 to treat IBS-D. The recommended dose is 100 mg taken orally twice daily with food. Although eluxadoline was associated with clinically meaningful improvements in stool consistency and urgency, it had less effect on abdominal pain. Thus, eluxadoline may be more ideal in patients with IBS-D with predominant and bothersome diarrhea than in those with predominant or more severe abdominal pain. Eluxadoline is associated with increased risk for pancreatitis (in patients without a gallbladder) and sphincter of Oddi dysfunction (in patients with a history of alcohol misuse). Thus, eluxadoline is contraindicated in patients without a gallbladder and those with excessive alcohol misuse as well as a history of sphincter of Oddi dysfunction, pancreatitis, bile duct obstruction, or severe liver impairment (51).

In 2 phase 3 RCTs (n = 1617 patients with IBS-D), treatment with eluxadoline compared with placebo was associated with improved abdominal pain and stool consistency (RR, 0.87 [CI, 0.83 to 0.92]). Compared with placebo, eluxadoline was associated with decreased episodes of incontinence and urgency (a greater proportion of responders for ≥50% urgency-free days; RR, 0.84 [CI, 0.78 to 0.90]) and a clinically meaningful improvement in IBS-QOL questionnaire score (RR, 0.84 [CI, 0.74 to 0.95]) during the 3-month treatment period (39). Similar results for all outcomes were seen at week 26.

New drugs in development address a "symptom-based" or "hypothesis-based" treatment approach to IBS. Drugs that focus on control of abdominal pain and stool frequency include olorinab (a cannabinoid receptor 2 agonist) (52), crofelemer (a botanical) (53), and ORP 101 (an opioid receptor agonist/antagonist) (54). Ebastine (an antihistamine) (55), ibodutant (a tachykinin NK2 receptor antagonist) (56), and solabegron (a β3-adrenergic receptor agonist) focus on altering the pathophysiology of IBS. Finally, fecal transplantation, microbiome manipulation via live bacterial products (MRx1234 [Blautix]), and sacral nerve stimulation are also being explored (57).

Is there evidence to support the effectiveness of herbal treatments?

Patients with IBS frequently try nontraditional or herbal therapies, particularly if traditional approaches to treatment do not relieve their symptoms. Although many herbal therapies are marketed for IBS, only STW5 (Iberogast) (58), peppermint oil (59), Padma Lax (60), and traditional Chinese medicine (61) have shown promise in clinical trials (**Appendix Table**, available at Annals.org). The quality of evidence supporting use of these medications is very low. Future high-quality trials of herbal remedies are needed.

What components of care should clinicians integrate into follow-up?

Clinicians should emphasize to patients that long-term prognosis is good, which may help reduce distress and anxiety. The typical symptom course in IBS is chronic and fluctuating. A commonsense approach includes monitoring for alarm features and progression of symptoms and managing psychosocial stressors. Clinicians should consider additional diagnostic tests or referral to specialty care if alarm features develop or if symptoms are refractory and persistent.

When should clinicians consider consulting a specialist?

When management strategies are not effective, clinicians should consider consulting a gastroenterologist. Gastroenterologists may have greater knowledge of treatment options because of their increased familiarity with IBS. Clinicians should consider referral to a mental health professional for patients with refractory symptoms leading to impaired quality of life or major depression, anxiety disorder, or somatization disorders.

Treatment... General measures, such as establishing an effective patient–clinician relationship, educating patients about IBS, and implementing lifestyle changes (including dietary advice, physical activity, and stress management), are essential to effective IBS management. If lifestyle changes do not completely relieve IBS symptoms, several medications may be helpful. Pharmacologic therapy should target the individual patient's symptom pattern, and options include antispasmodics, laxatives, antidiarrheal agents, manipulation of microflora, and several FDA-approved IBS-specific drugs. Central neuromodulators are an essential treatment in managing IBS when symptoms, particularly pain, are dominant or when there are psychological comorbidities.

CLINICAL BOTTOM LINE

Practice Improvement

What do professional organizations recommend for the care of patients with IBS?

Several clinical practice guidelines have been developed to help clinicians manage patients with IBS. These include the American Gastroenterological Association guidelines on pharmacologic management of IBS with constipation (45) and diarrhea (39), the American College of Gastroenterology guidelines on management of IBS (13), the Canadian Association of Gastroenterology guidelines (14), and the 2017 National Institute for Health and Care Excellence guidelines from the United Kingdom (34).

Are there performance measures related to the care of patients with IBS?

The quality of the physician–patient interaction is paramount to effective management of IBS. A strong therapeutic relationship helps patients feel validated and empowered to manage their condition, which can lead to better symptom control, improved patient satisfaction, and reduced health care utilization. Current proposed performance measures in the United States do not include any measures specifically related to the care of patients with IBS.

In the Clinic
Tool Kit

Irritable Bowel Syndrome

Patient Information

https://medlineplus.gov/irritablebowelsyndrome.html
https://medlineplus.gov/languages/irritablebowelsyndrome.html
Information on irritable bowel syndrome in English and other languages from the National Institutes of Health's MedlinePlus.

https://gi.org/topics/irritable-bowel-syndrome
Resources on irritable bowel syndrome from the American College of Gastroenterology.

https://patient.gastro.org/irritable-bowel-syndrome-ibs
American Gastroenterological Association patient information center on irritable bowel syndrome.

www.niddk.nih.gov/health-information/digestive-diseases/irritable-bowel-syndrome

www.niddk.nih.gov/health-information/informacion-de-la-salud/enfermedades-digestivas/sindrome-intestino-irritable
Health information on irritable bowel syndrome in English and Spanish from the National Institute of Diabetes and Digestive and Kidney Diseases.

Information for Health Professionals

https://gastro.org/clinical-guidance/pharmacological-management-of-irritable-bowel-syndrome-with-diarrhea-ibs-d
American Gastroenterological Association clinical guidelines on pharmacologic management of irritable bowel syndrome with diarrhea.

https://gastro.org/clinical-guidance/pharmacological-management-of-irritable-bowel-syndrome-with-constipation-ibs-c
American Gastroenterological Association clinical guidelines on pharmacologic management of irritable bowel syndrome with constipation.

https://gastro.org/clinical-guidance/the-role-of-diet-in-irritable-bowel-syndrome-ibs
American Gastroenterological Association clinical practice update on the role of diet in irritable bowel syndrome.

https://journals.lww.com/ajg/Fulltext/2021/01000/ACG_Clinical_Guideline__Management_of_Irritable.11.aspx
American College of Gastroenterology clinical guideline on the management of irritable bowel syndrome.

https://academic.oup.com/jcag/article/2/1/6/5290372
Canadian Association of Gastroenterology clinical practice guideline for the management of irritable bowel syndrome.

www.nice.org.uk/guidance/cg61
National Institute for Health and Care Excellence clinical guideline on the diagnosis and management of irritable bowel syndrome in adults.

WHAT YOU SHOULD KNOW ABOUT IRRITABLE BOWEL SYNDROME

What Is Irritable Bowel Syndrome?

Irritable bowel syndrome (IBS) is a problem that affects your large intestine. Symptoms include stomach pain, cramps, discomfort, bloating, and abnormal bowel movements. It is more common in women than in men. Its exact cause is unknown.

What Are the Symptoms?

People with IBS can have many different symptoms. In general, IBS can cause stomach pain or discomfort that happens along with diarrhea, constipation, or both. Other symptoms may include:

- An abnormal number of bowel movements (>3 per day or <3 per week)
- Urgency of bowel movements
- Straining during bowel movements
- Feeling that a bowel movement is not finished
- More gas than usual
- Tiredness
- Muscle pain
- Trouble sleeping

If these symptoms occur with weight loss, fever, blood in the stool, or recent use of antibiotics, IBS is usually not the cause.

How Is It Diagnosed?

There is no specific test for IBS. Your doctor will ask you about your medical history and your symptoms and may do a physical examination to make a diagnosis. Endoscopy or imaging tests, such as CT scans, are usually not needed to diagnose IBS. Your doctor may ask you to have certain tests to make sure there is not another disease causing the symptoms, especially if you have any of the following:

- Weight loss, bloody stool, fever, or waking up at night due to pain
- Recent use of antibiotics
- A family history of colon cancer or inflammatory bowel disease

How Is It Treated?

Changing what you eat can sometimes help. Foods to avoid include:

- Fatty foods
- Certain vegetables, like beans, cabbage, broccoli, and cauliflower

- Drinks with a lot of caffeine or carbonation (such as soda)
- Foods that are very high in fiber (which can cause gas or bloating)
- Foods that are low in fiber (which can cause constipation)

Other possible ways to treat IBS include:

- Stress management, including via counseling, meditation, regular exercise, yoga, or getting enough sleep
- Behavioral therapies (if the IBS is related to a psychological condition)
- Medicines that target your symptoms

Questions for My Doctor

- What can trigger IBS?
- What foods or drinks should I stay away from?
- What other lifestyle changes do I need to make?
- Is there a medicine I can take to treat my symptoms?
- What are the side effects of the medicine I will be taking?
- Could stress be causing my IBS?
- Should I have an imaging study to see if it really is IBS?

For More Information

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MedlinePlus
https://medlineplus.gov/irritablebowelsyndrome.html

American Academy of Family Physicians
https://familydoctor.org/condition/irritable-bowel-syndrome-ibs

American Gastroenterological Association
https://patient.gastro.org/irritable-bowel-syndrome-ibs

Patient Information

Appendix Table. **Alternative and Herbal Therapies for IBS**

Therapy	*Description*	*Notes (Reference)*
Peppermint oil	Inhibits smooth-muscle contraction and functions as an antispasmodic	Multiple RCTs show superiority to placebo for global improvement of symptoms and improvement in abdominal pain. The most common adverse effect was heartburn (56).
STW5 (Iberogast)	A liquid multidrug herbal supplement containing bitter candytuft, angelica root, chamomile flowers, caraway fruit, St. Mary's thistle, lemon balm leaves, peppermint leaves, celandine, and licorice root	Several studies have been done in functional gut disorders. In 1 RCT, STW5 was associated with a reduction in abdominal pain and global symptoms (55).
Padma Lax	Tibetan herbal formula	Associated with improvement in global symptoms in 1 RCT ($n = 61$) (57)
Traditional Chinese medicine	Herbal formula consisting of multiple dried herbs	In 1 RCT ($n = 119$), a standard Chinese herbal formula and an individualized formula designed by a Chinese medical herbalist were associated with improvement in symptoms (58).

IBS = irritable bowel syndrome; RCT = randomized controlled trial.