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Diagnosis and Treatment of Irritable Bowel Syndrome
A Review

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IMPORTANCE The prevalence of irritable bowel syndrome (IBS) in the United States is between 7% and 16%, most common in women and young people, with annual direct costs estimated at more than $1 billion dollars in the United States. Traditionally, the diagnosis of IBS has been based on the positive identification of symptoms that correlate with several different syndromes associated with disorders such as IBS diarrhea, IBS constipation, functional diarrhea, functional constipation, chronic functional abdominal pain, or bloating. Several peripheral and central mechanisms initiate gastrointestinal motor and sensory dysfunctions leading to IBS symptoms. Those dysfunctions may require evaluation in patients whose symptoms do not respond to first-line treatments.

OBSERVATIONS Validation studies of consensus symptom-based criteria have identified deficiencies that favor a simpler identification of the predominant symptoms of abdominal pain, bowel dysfunction, and bloating and exclusion of alarm symptoms such as unintentional weight loss, rectal bleeding, or recent change in bowel function. Symptom-based diagnosis of IBS is enhanced with additional history for symptoms of somatoform and psychological disorders and alarm symptoms, physical examination including digital rectal examination, and screening tests to exclude organic disease (by measuring hemoglobin and C-reactive protein concentrations). The initial treatment plan should include patient education, reassurance, and first-line treatments such as fiber and osmotic laxatives for constipation, opioids for diarrhea, antispasmodics for pain and for management of associated psychological disorders. For patients who do not respond to those IBS treatments, testing for specific functional disorders may be required in a minority of patients with IBS. These disorders include rectal evacuation disorder, abnormal colonic transit, and bile acid diarrhea. Their identification is followed by individualized treatment, such as pelvic floor retraining for rectal evacuation disorders, sequestrants for bile acid diarrhea, and secretory agents for constipation, although there is only limited evidence that this individualized management approach is effective.

CONCLUSIONS AND RELEVANCE Advances in the identification of specific dysfunctions as causes of individual symptoms in the "IBS spectrum" leads to the potential to enhance the diagnosis and management of symptoms for the majority of patients for whom first-line therapies of IBS and management of comorbid psychological disorders are insufficient.

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Irritable bowel syndrome (IBS) is a chronic disorder of bowel function characterized by altered bowel function (frequency and/or consistency) and abdominal pain related to the function of the bowel.[1] IBS can greatly affect patients, reducing their quality of life and work productivity. The prevalence of IBS in the United States ranges between 7% and 16%, and the condition is most common in women and young people; annual direct costs associated with IBS have been estimated at more than $1 billion in the United States.[2,3] Epidemiological surveys show that women have a slightly higher global prevalence of 12% (95% CI, 9.3%-15%) vs 8.6% (95% CI, 6.3%-11.2%) than do men (odds ratio [OR], 1.46; 95% CI, 1.33-1.59).[4] However, compared with men, women more often seek health care services, including tertiary and ambulatory care for IBS and other functional bowel disorders by a ratio of 2 to 2.5 to 1.[5]

IBS is commonly attributed to disorders of gut-brain interactions. Several centrally mediated processes resulting in visceral hypersensitivity and peripheral mechanisms that initiate perturbations of gastrointestinal motor and sensory functions have been recognized and can lead to IBS symptoms.[6] In general, it is important to identify patients with somatoform disorders such as tension headaches or arthralgias and psychological symptoms of anxiety or depression because the early use of behavioral psychotherapy, hypnotherapy, or central neuromodulators can help alleviate IBS severity. In the last decade, research studies have identified peripheral irritants or mechanisms that cause the dysfunction leading to IBS symptoms. Although these mechanisms, discussed in this article, provide an opportunity to explain the etiology of symptoms to patients and may be used to reverse symptoms of IBS, there is

Box 1. Commonly Asked Questions About IBS

Are There Diagnostic Tests for IBS?
There are no single or specific diagnostic tests for irritable bowel syndrome (IBS). IBS represents a spectrum of symptoms that may arise from diverse dysfunctions of the gut-brain axis, including abnormal intestinal motility or transit, increased sensation or perception of abdominal symptoms such as pain or bloating (mediated in the gut or in the brain), and psychological disturbances including somatization or multiple somatic comorbidities. Tests to exclude organic diseases such as colon cancer, inflammatory bowel disease, or celiac disease are recommended according to guidelines for screening for colon cancer or the presence of alarm features such as weight loss or rectal bleeding. A history of rectal bleeding, weight loss, nocturnal diarrhea; symptoms suggestive of somatoform or psychological disorders such as anxiety or depression; and screening blood tests such as hemoglobin and C-reactive protein enhance the diagnostic performance of symptom-based criteria for IBS.

What Medications Should Be Started First for IBS?
The first-line treatments for IBS are fiber (preferably ispaghula husks) and osmotic laxatives such as saline laxatives or polyethylene glycol 3350 for constipation, loperamide for diarrhea, and antispasmodics such as hyoscine for cramping abdominal pain. When there are prominent psychological symptoms or multiple somatic comorbidities, a neuromodulator such as a low-dose tricyclic agent such as amitriptyline may be used as a first-line treatment.

When and What Specialized Tests May Be Indicated for IBS?
Although there are no single or specific diagnostic tests for IBS, if patients do not respond to first-line treatments for the primary symptoms of diarrhea, constipation, or pain or discomfort, careful reassessment of the history and physical examination may suggest a need for additional tests to identify treatable dysfunctions. These tests include anorectal manometry and balloon expulsion, colonic transit, and tests for biochemical causes of diarrhea including sugar malabsorption, bile acid diarrhea. However, there is limited evidence from large trials proving effectiveness of treatment of these disorders when they are identified. Cumulative evidence from several small trials suggests efficacy of pelvic floor retraining with biofeedback for patients with pelvic floor dyssynergia presenting with symptoms of IBS constipation (IBS-C) or functional constipation.

Are There Nonpharmacological Approaches for IBS?
In addition to fiber supplementation (ispaghula tusks preferred to bran) for constipation, dietary exclusions of several sugars, the low FODMAP (fructans, oligosaccharides, disaccharides, monosaccharides, and polyols) diet and microbial modification using pre- and probiotics or fecal microbial transplant may be considered; however, evidence supporting these approaches is limited. Psychotherapeutic and alternative medicine approaches such as acupuncture may also be indicated.

What Medications Are Approved in the US for the Treatment of IBS?
Lubiprostone, linaclotide, plecanatide, and tenapanor are approved for IBS-C in adults. Tegaserod is approved for women younger than 65. Polyethylene glycol (PEG) 3350 is approved for the treatment of occasional constipation. Alosetron is indicated only for women with severe IBS-D who have not responded adequately to conventional therapy. The US Food and Drug Administration has not approved any drugs solely for the pain component of IBS.

limited evidence from large trials proving effectiveness of treatment directed to these disorders when they are identified.

The objectives of the article are to review the advances in the diagnosis and treatment of IBS, particularly applying current knowledge to explore the role of disorders of evacuation and chemical irritants and to assess the current role of bacterial overgrowth, and therapeutics including dietary, pharmacotherapy, psychotherapy, and microbial treatment in the clinical management of IBS.

Methods

A literature search for English-language systematic reviews and guidelines regarding the diagnosis and treatment of IBS was performed in PubMed and the Cochrane Database of Systematic Reviews from 1980 to September 1, 2020. PubMed was searched using the narrow diagnosis and therapy clinical queries and the systematic review filter. Only diagnosis and treatment approaches currently available in clinical practice were included. Because of the strength of the evidence, this included medications not yet approved in the United States, specifically otilonium, pinaverium, cimetropium, and elobixibat, and the tauroselcholic (selenium 75) acid (^{75}SeHCAT) diagnostic test for bile acid malabsorption.

Based on these search criteria, 112 articles were included and serve as the basis for this review, including 25 clinical trials, 26 reviews, 33 original articles, 3 network meta-analyses, 3 systematic reviews, and 24 systematic reviews and meta-analyses (**Box 1**).

Clinical Presentation

Patients typically present to their primary care clinicians with various combinations of 4 main symptoms: abdominal discomfort or pain, diarrhea, constipation, and bloating. There may be other symptoms suggestive of functional gastrointestinal disorders including postprandial upper abdominal discomfort, fullness, nausea (and less commonly, vomiting), and heartburn. Based on a 2001 population-based survey designed to determine the prevalence of IBS, 58% of patients sought care for their abdominal symptoms from a family physician or general practitioner and 49% sought care from a gastroenterologist in the prior 12 months for their abdominal symptoms.[7] In 2014, there were 585 061 outpatient visits and 18 638 emergency department visits with the indication of IBS and 70 963 hospital admissions for functional or motility disorders in the United States.[3] In 2015, health care expenditures for abdominal pain were estimated to be $10.2 billion.[3]

Diagnosis

Symptom-Based Criteria

A sequence of consensus-based Rome criteria for IBS has been published since 1989[8-11] (**Box 2**).[12] The fundamental definition based on abdominal pain in association with bowel dysfunction has been consistent across the 4 versions of the criteria. However, 2 major changes occurred in the Rome II and IV criteria. The changes that led to the Rome II criteria in 1999[9] involved clarification of definitions, and splitting off in to additional diagnostic categories

Box 2. Summary of Rome I Through IV Irritable Bowel Syndrome Criteria[a]

Rome I[b]

The Rome I criteria, developed by consensus in 1989, defined irritable bowel syndrome (IBS) as continuous or recurrent symptoms of abdominal pain relieved with defecation or associated with a change in frequency or consistency of stool—disturbed defecation (≥2) (1) altered stool frequency, (2) altered stool form (hard or loose/watery), (3) altered stool passage (straining or urgency, feeling of incomplete evacuation), and (4) passage of mucus—usually with bloating or feeling of abdominal distension.

Rome II[c]

Functional bowel disorders recognized diverse IBS, functional abdominal bloating, functional constipation, functional diarrhea, unspecified functional bowel disorder. IBS criteria symptoms are defined as lasting at least 12 weeks, which need not be consecutive, in the preceding 12 months of abdominal discomfort or pain that includes at least 2 of the following: (1) relieved with defecation, (2) onset associated with a change in frequency of stool, or (3) onset associated with a change in form (appearance) of stool.

Rome II "Splitting" of Non-IBS Criteria

In 1999, the Rome II split off symptoms into additional categories such as alterations in bowel function or bloating that were not consistently associated with pain. To meet the IBS criteria, symptoms must be at least 12 weeks, which need not be consecutive, in the preceding 12 months of

Functional Abdominal Bloating

Feeling of abdominal fullness, bloating, or visible distension or insufficient criteria for a diagnosis of functional dyspepsia, IBS, or other functional disorder

Functional Constipation

Includes the following symptoms: straining, lumpy or hard stools, sensation of incomplete evacuation, sensation of anorectal obstruction or blockade in >1 of 4 defecations, manual maneuvers to facilitate >1 of 4 defecations (eg, digital, evacuation, support of the pelvic floor), or <3 defecations a week

Loose Stools

Loose stools are not present, and there are sufficient criteria for IBS

Functional Diarrhea

Liquid (mushy) or watery stools, present for > three-fourths of the time, and no abdominal pain.

Rome III[d]

In 2006, Rome III criteria defined functional bowel disorders as including IBS, functional bloating, functional constipation, functional diarrhea, and unspecified functional bowel disorder.

IBS

Rome III criteria defined IBS as recurrent abdominal pain or discomfort (an uncomfortable sensation not described as pain) for at least 3 days per month in the last 3 months associated with ≥2 of the following: improvement with defecation, onset associated with a change in frequency of stool, onset associated with a change in form (appearance) of stool, and criteria fulfilled for the last 3 months with symptom onset of ≥6 months prior to diagnosis.

Subtyping IBS by Predominant Stool Pattern

IBS-C (constipation): hard or lumpy stools for ≥25% of bowel movements and loose (mushy) or watery stools <25%

IBS-D (diarrhea): loose (mushy) or watery stools for ≥25% of bowel movements and hard or lumpy stool for <25%

IBS-M (mixed): hard or lumpy stools for ≥25% of bowel movements and loose (mushy) or watery stools for ≥25%

Unsubtyped IBS: insufficient abnormality of stool consistency to meet criteria for subtypes IBS-C, D, or M

Functional Constipation

Functional constipation is defined as ≥2 of the following: straining during ≥25% of defecations, lumpy or hard stools in ≥25% of defecations, sensation of incomplete evacuation for ≥25% of defecations, sensation of anorectal obstruction for ≥25% of defecations, manual maneuvers to facilitate ≥25% of defecations (eg, digital, evacuation, support of the pelvic floor), <3 defecations per week, loose stools are rarely present without the use of laxatives, or insufficient criteria for IBS

Functional Diarrhea

Functional diarrhea is defined as loose (mushy) or watery stools without pain in ≥75% of stools and the criteria fulfilled for the last 3 months with symptom onset ≥6 months before diagnosis.

Rome IV[e]

In 2016, the Rome IV criteria for functional bowel disorders recognized IBS, functional abdominal bloating and distension, functional constipation, functional diarrhea, unspecified functional bowel disorder, opioid-induced constipation.

IBS

IBS is defined as recurrent abdominal pain, on average, at least 1 day per week in the last 3 months and is associated with ≥2 of the following criteria: related to defecation, associated with a change in frequency of stool, associated with a change in form (appearance) of stool, and the criteria fulfilled for the last 3 months with symptom onset ≥6 months before diagnosis

Diagnostic Criteria for IBS Subtypes

Predominant bowel habits are based on stool form on days with at least 1 abnormal bowel movement.

IBS-C: >25% of bowel movements with Bristol Stool Form Scale (BSFS) types 1 or 2 and <25% with BSFS types 6 or 7

IBS-D: >25% of bowel movements with BSFS types 6 or 7 and <25% with BSFS types 1 or 2

IBS-M: >25% of bowel movements with BSFS types 1 or 2 and >25% with BSFS types 6 or 7

IBS-U: an unclassified subcategory that meets criteria for IBS, but bowel movements cannot accurately be categorized into 1 of the 3 subgroups

[a] Adapted from Camilleri et al.[12]

[b] Adapted from Thompson et al.[8]

[c] Adapted from Thompson et al.[9]

[d] Adapted from Longstreth et al.[10]

[e] Adapted from Lacy et al.[11]

of symptoms that were not consistently associated with pain, such as functional constipation, diarrhea, and bloating as well as functional abdominal pain syndrome, characterized by at least 6 months of pain with poor relation to gut function and loss of daily activities. The Rome III criteria of 2006[10] then required characteristic symptoms to be present during the 3 months and onset for 6 or more months prior to presentation and essentially retained the subtyping of IBS based on bowel function, particularly stool consistency. In the Rome IV criteria of 2016,[11] the main changes have been the exclusion of discomfort (in contrast to pain) as a symptom and required the more stringent frequency criteria for pain to be eligible for diagnosis of IBS (specifically, on average, at least 1 day per week in the last 3 months). Box 2 shows a summary of the main characteristics in the 4 iterations of the Rome criteria for IBS and its subtypes. Although the fundamental definition of IBS based on abdominal pain in association with bowel dysfunction has been consistent throughout the Rome criteria iterations, there are differences in the diagnostic performance in each iterations of the criteria.[13]

In one study,[14] the positive likelihood ratio and specificity for identifying IBS among 318 patients with lower gastrointestinal (GI) tract symptoms improved by combining the Rome III diagnostic criteria with 3 approaches: (1) assessing patients' alarm symptoms such as unintentional weight loss, rectal bleeding, or recent change in bowel function; (2) obtaining additional history, specifically, asking about the presence of nocturnal stools, symptoms suggestive of multiple somatic comorbidities and psychological disorders (especially affective disorders); (3) conducting a limited diagnostic evaluation including complete colonoscopy to cecum or terminal ileum, and measuring hemoglobin and C-reactive protein (CRP) levels.

Symptom-based criteria cannot be used alone to establish a diagnosis of IBS. Limited testing is required to exclude conditions that mimic IBS including colorectal cancer, among patients 40 years or older presenting for the first time, or celiac disease. Patients older than 40 years should be investigated in accordance with colon cancer screening guidelines.[15-17] However, clinical experience, demonstrates that there is the significant overlap between different diagnostic groups. For example, the symptoms of IBS constipation (IBS-C) overlap those of functional constipation. In addition, there is transition within the same patient between different clusters of symptoms such as transition between IBS and functional dyspepsia or between IBS diarrhea (IBS-D) and functional diarrhea,[18-21] and similar responses to the same treatments based on targeting the bowel dysfunction lead to the proposal[12] of a simpler approach focusing on the predominant symptom (**Figure**).

The proposed algorithm (Figure) focuses on the predominant symptoms of pain, constipation, or diarrhea within the IBS symptom complex, rather than attempting to fit the patients into one or more formulaic symptom clusters that combine bowel dysfunction (diarrhea, constipation, mixed, or paradoxically unspecified), abdominal pain, and bloating (Box 2). Prospective studies are, however, required to compare the clinical utility of the traditional approach based on management of IBS cluster or symptoms with focusing on individual symptoms.

Patient History

The Figure shows a recommended sequence in assessing whether patients have IBS. While taking a patient's history, IBS symptoms associated with bowel dysfunction such as bloating and abdominal pain should be identified; patients with constipation also tend to experience bloating and pain before and after passage of bowel movements. To differentiate IBS from diseases that mimic it, the history should include asking about nocturnal diarrhea; straining to evacuate; or somatic comorbidities, including psychological disorders, bladder symptoms, or a family history of dietary intolerance of certain foods or celiac disease. To screen for rectal evacuation disorders, clinicians should ask about bladder symptoms,[22] such as whether patients experience sensations of incomplete bladder evacuation, increased urinary frequency, recurrent urinary tract infections, or nocturia or whether patients experience the need to strain or digitate the anal canal or vagina or support the perineum to facilitate evacuation of stool.

Physical Examination

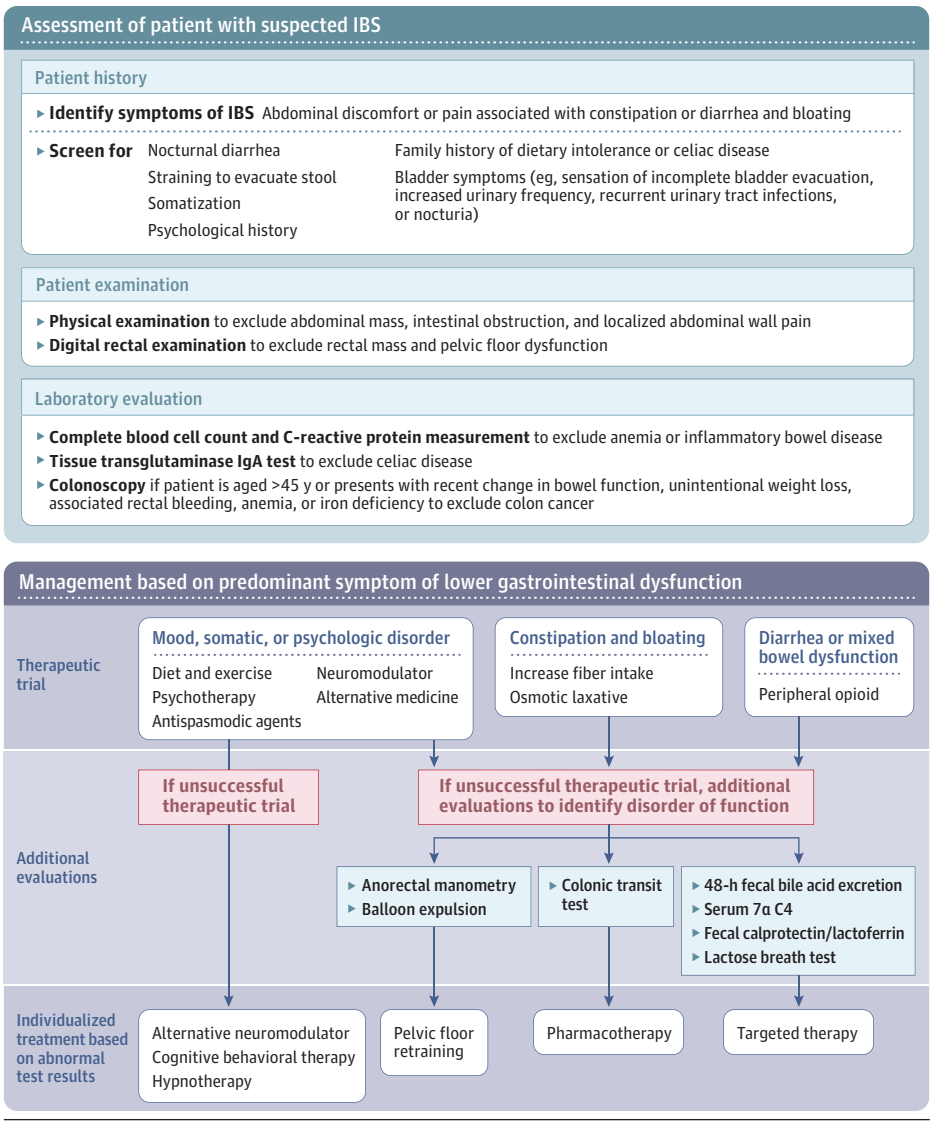
The physical examination should exclude abdominal mass, signs of intestinal obstruction, or the Carnett sign for localized abdominal wall pain that remains unchanged or increases when the muscles of the abdominal wall are tensed, suggesting a somatic rather than an intraabdominal source of pain. In addition, the degree of lumbar lordosis while lying supine may provide an explanation for perceived abdominal distension in patients with bloating. However, conducting a digital rectal examination is a very important way[23] to identify signs suggestive of pelvic floor dysfunction such as inadequate perineal descent during straining, high resting anal sphincter pressure, paradoxical contraction of the pelvic floor while attempting to expel the examining finger from the rectum,[24,25] and puborectalis tenderness that suggests associated pelvic myofascial pain[26] that contributes to lower abdominal and pelvic pain.

Laboratory Evaluation

Investigations are geared to exclude underlying diseases and identify specific functional disorders resulting in IBS symptoms. Typically, these include a complete blood cell count; C-reactive protein measurement to exclude anemia (which might be associated with colon cancer) or inflammatory bowel disease; and serological testing to screen for celiac disease. For the latter approach, a meta-analysis and systematic review of 36 studies involving patients with suggested IBS were compared with healthy controls to test for celiac disease. The study found that biopsy-confirmed celiac disease was associated with any of the IBS subtypes compared with controls,[27] although a recent study involving 289 patients undergoing duodenal biopsy in an open-access endoscopy practice with the indication of chronic diarrhea showed only 5% positive results for celiac disease or other rare diseases such as mastocytosis or eosinophilic gastroeneritis.[28]

In fact, timely inclusion of valid function tests has the potentioal to reduce health care utilization, as documented in 936 patients with chronic diarrhea who had completed, on average 1.2 transaxial imaging, 26 endoscopic procedures, and 1.6 miscellaneous tests per person before undergoing fecal bile acid test.[29] Most importantly, there is an opportunity for use of thorough history, digital rectal examination, and clinically available relatively inexpensive approaches to identify specific dysfunctions that are amenable to individualized therapy for symptoms of IBS.[30]

Figure. Suggested Algorithm for Diagnosis of IBS and Associated Entities Based on Predominant Symptoms and Utilizing Tests to Identify Plausible Mechanisms for the Symptoms



This approach requires further validation and assessment of generalizability. 7α C4 indicates 7α-hydroxy-4-cholesten-3-one; IBS, irritable bowel syndrome.

Treatment Approaches

After physical examination and screening for organic diseases, a practical algorithm is based on the specific predominant symptom of lower gastrointestinal dysfunction. For the first-line of therapy, as well as for subsequent steps in the algorithm, treatment should be based on the predominant symptom. Patients who do not respond to the first-line therapy should be evaluated for possible organic dysfunction(s).

No compelling evidence exists to suggest that patients with suspected IBS should routinely undergo colonoscopy. Thus, in a cross-sectional study involving 466 patients with nonconstipated predominant IBS (IBS-D, or mixed [IBS-M], stools that vary from being hard or loose; Box 2) who underwent colonoscopy, no cases of colorectal cancer were detected, and inflammatory bowel disease was observed in less than 2% of the patients.[31] Similarly, in a study in an open access setting involving 469 consecutive patients who underwent colonoscopy, which was performed at the request of referring physicians without a gastroenterology subspecialist consultation and underwent ileoscopy with biopsies to investigate the cause of chronic diarrhea, 17.6% of the entire cohort tested positive for colonic disease: 10.6% had microscopic colitis and 4.5% had other forms of colitis such as Crohn disease or ulcerative colitis. Of 159 patients, 16 (10%) had abnormal ileal biopsy results.[28]

However, screening guidelines recommend colonoscopy for Black patients older than 45 years, patients older than 50 years,[32] and patients who present alarm symptoms or signs (such as recent change in bowel function, unintentional weight loss, associated rectal bleeding, or anemia or iron deficiency on complete blood cell count).

Once patients are initially assessed, have undergone simple screening tests (Figure), and are told they have IBS, they should be reassured, educated, and encouraged to make lifestyle changes such as developing relaxation techniques (eg, diaphragmatic breathing) and engaging in exercise. Education about these disorders of function and establishment of an effective

patient-physician relationship are key to effective management. Specifically, providing the patient with a model of their problem as a brain-gut disorder is helpful.[33]

A randomized clinical trial (RCT)[34] involving 102 patients and its follow-up study[35] (median follow-up of 39 patients, 5.2 years) found that patients who had engaged in vigorous physical activity 3 to 5 days a week over 12 weeks experienced a reduction in IBS and psychological symptoms. Another study,[36] reported that yoga tended to reduce severity of IBS and somatic symptoms and that walking improved overall GI symptoms, negative affect, and anxiety. Other simple approaches include teaching patients general relaxation techniques including diaphragmatic breathing.

First-line Pharmacological Treatments

First-line pharmacological treatments based on symptoms include spasmolytic or antispasmodic agents, such as sublingual hyoscyamine for pain, loperamide for diarrhea or mixed-bowel dysfunction, and dietary fiber (≤20 g/d) and osmotic laxative for constipation. The loperamide treatment may be used on an as-needed basis, especially among patients with mixed-bowel dysfunction, in whom there is evidence that, as a group, their colonic transit measured over 48 hours is similar to that of patients with IBS-D.[37]

When the patient has features suggestive of mood disorders, somatization, or multiple somatic comorbidities and a dominant symptom of pain, the features are consistent with functional abdominal pain syndrome or as termed in the Rome IV criteria, *centrally mediated abdominal pain syndrome*.[38] Specific treatment for this group is based on neuromodulators[39] and is also discussed below.

Second-line Pharmacological Treatments

If a patient does not respond to these first-line approaches, other tests may be indicated as shown in the Figure and detailed below, such as anorectal manometry, colonic transit tests, and serum and fecal biochemical tests to identify specific disorders that make the patients candidates for specialized treatment. These tests are not generally available in general or internal medicine practice; however, they broadly fulfill 5 plausibility criteria articulated by a consensus of experts:

1. the presence of the abnormality in a subset of patients,
2. temporal association between proposed mechanism and symptom(s),
3. correlation between the level of impairment of mechanism and symptom(s),
4. induction of the symptoms(s) by provoking the pathophysiological abnormality in healthy subjects,
5. treatment response by a therapy specifically correcting the underlying disorder or congruent natural history of symptoms and dysfunction in the absence of specific therapy.[40]

Patients with predominant constipation, bloating, or both who have severe symptoms or a history or rectal examination suggesting a rectal evacuation disorder should undergo further tests based on the measurement of colonic transit with radiopaque markers[41-43] or scintigraphy[44,45] or wireless motility capsule[46] and high-resolution anorectal manometry with balloon expulsion.[47] A recently recognized feature[30,48,49] of obstruction to defecation is the identification on plain abdominal radiography of a "bubble" of gas larger than 9 cm^2 with or without stool in the pelvis between the superior border of the pubic symphysis and the lower end of the sacroiliac joints. Often such abdominal radiographs are performed to exclude other causes of abdominal or flank pain such as renal calculi. This finding can assist internists and gastroenterologists identify which patients with chronic constipation (typically with features such as excessive straining or sense of incomplete evacuation) should be referred for specialized tests, such as anorectal manometry and balloon expulsion tests. Rectal evacuation disorders are also associated with abdominal bloating and distension.[50] The abdominal radiograph also identifies the burden of stool in the colon, and serves to confirm the symptoms related to constipation.[51]

For patients with diarrhea or mixed bowel dysfunction, further testing may include measurement of colonic transit, as described above. However, other commonly encountered conditions, supported by the history, such as having a family history of dietary intolerances or antecedent history predisposing to bile acid diarrhea such as cholecystectomy or taking medications predisposing to microscopic colitis (eg, proton pump inhibitors) will inform the choice of other tests. Epidemiologically, lactase deficiency is extremely relevant, given that approximately 65% of the human population has a reduced ability to digest lactose after infancy, and lactose intolerance in adulthood is most prevalent in people of East Asian descent, affecting more than 90% of adults in some of these communities.[52,53] Far less prevalent is sucrase-isomaltase deficiency, which typically presents in childhood, but patients with IBS may harbor rare pathological genetic variants in the sucrase-isomaltase gene.[54] Either a diet excluding the suspected sugar intolerance[55] or breath test with the appropriate substrate such as lactose or sucrose can be used to confirm these sugar intolerances.

Testing for fecal calprotectin or lactoferrin are indicated before ordering a colonoscopy to rule out inflammatory bowel disease in patients with nonbloody diarrhea.

Testing for bile acid diarrhea may be another line of investigation. Based on a systematic review and meta-analysis, about 25% of patients with IBS-D or functional diarrhea have bile acid diarrhea.[56] The main diagnostic tool until recently was administering the ^{75}SeHCAT retention test (unavailable in the United States) or a therapeutic trial with a bile acid sequestrant. This has become more relevant in clinical practice in the United States, since biochemical tests to confirm the diagnosis have become available,[57] specifically, patients could undergo the 48-hour fecal total and primary bile acid excretion or their blood is assayed after a fast (before 10 AM) for serum 7α-hydroxy-4-cholesten-3-one (7α C4) concentration in nanograms per milliliter, a measurement of hepatic bile acid synthesis that correlates positively with fecal bile acid excretion. Measurement of fecal elastase to screen for pancreatic exocrine insufficiency may be indicated, especially if the loose stools suggest fat malabsorption, such as bulky or greasy stools. However, the utility of this test for the vast majority of patients with IBS-D is questionable.

Although the medical literature suggests an etiological role of small intestinal bacterial overgrowth among patients with IBS, this possibility remains uncertain.[58] The use of glucose or lactulose breath test for diagnosis is reported as a conditional recommendation in the American College of Gastroenterology Clinical Guideline because of the low or very low level of evidence,[59] the lack of

control regarding the relationship between hydrogen peak and arrival of the substrate in the colon,[60] and the results of duodenal cultures that show no differences between IBS and controls when using the standard threshold of 10^5 colony-forming units per milliliter.[61] Two clinical trials involving 1260 patients reported that patients assigned to take rifaximin experienced adequate relief of IBS symptoms and that rifaximin's main clinical effect was on bloating rather than on IBS symptoms.[62]

The performance characteristics of these diverse tests for identifying abnormal results in the different phenotypes discussed has been recently published.[30] These include anorectal manometry (rectoanal pressure gradient); balloon expulsion test and rectal area on plain radiograph of the pelvis for rectal evacuation disorder; colonic transit and colonic stool burden score on abdominal x-ray for slow transit constipation or fast transit diarrhea; ^{75}SeHCAT retention at 7 days; 48-hour fecal bile acid excretion and fasting serum 7α C4 concentrations for bile acid diarrhea; and lactose breath test for carbohydrate maldigestion.

These results from a single center require replication at other centers, and the outcomes to treatment based on identification of the "organic dysfunction" still require development of therapeutic approaches including medications that effectively target the dysfunction(s) and validation in large clinical trials.

These novel data represent a possible future direction for identifying the underlying cause or mechanisms of symptoms associated with IBS. However, there are no large studies documenting the benefit of identifying the specific mechanism, with the exception of defecatory disorders in which pelvic floor retraining has been shown to be more effective for patients with pelvic floor dyssynergia-type constipation compared with treatments for constipation.[63-67] In relation to bile acid sequestration for bile acid malabsorption in patients with IBS-D, a placebo-controlled study[68] of colesevelam among 24 patients demonstrated mechanistic proof of efficacy (hepatic synthesis of bile acids, and colonic mucosal expression of genes that regulate bile acid responses) but not clinical efficacy, emphasizing the importance of having a sufficient sample size to demonstrate whether colesevelam is clinically beneficial. The utility of formal diagnosis of bile acid diarrhea is provided from clinical practice experience showing that bile acid sequestrant treatment of bile acid diarrhea based on positive biochemical diagnosis in 406 patients is associated with a 1.92-fold higher likelihood of clinical response compared with 61 patients given the same medication empirically without the benefit of positive biochemical diagnosis.[29]

Treatment

The main strategies for treatment for patients with IBS are dietary, psychotherapy, pharmacotherapy, and microbial therapies. This section relies on information from summaries documented in systematic reviews and meta-analyses.

Dietary Therapy

Dietary approaches to ease IBS symptoms has mixed results. A systematic review and meta-analysis[69] involving 15 RCTs and including 946 patients assessing effects of dietary fiber documented a statistically significant effect in favor of fiber compared with placebo (relative risk [RR] of IBS not improving, 0.87; 95% CI, 0.80-0.94) but reported no significant effect for bran, with the exception of ispaghula husks, which had significant effect in treating IBS symptoms (RR, 0.83; 73-0.94; number needed to treat [NNT], 7). However, a subsequent study of 5 RCTs (only 1 of which was reported to have a low risk of bias) that included evaluating ispaghula husks, found fiber had no significant benefit compared with placebo (RR, 0.78; 95% CI, 0.59-1,02).[70] Fiber supplementation may also be associated with aggravation of symptoms for some patients with IBS.[71]

Two RCTs of gluten rechallenge among patients whose IBS responded to gluten withdrawal found no statistically significant effect on IBS symptoms between the gluten challenge and the gluten-free diet (RR, 0.46; 95% CI, 0.16-1.28); 39 of 54 patients (72.2%) on the gluten diet and 12 of 52 patients (23%) on the gluten-free diet were symptomatic; however, there was significant heterogeneity between the 2 small studies with total sample sizes of 34 and 72,[69] so larger studies are required.

Since 2015, the UK National Institute of Clinical Excellence (NICE)[72] has strongly recommended the low FODMAP (fermentable oligosaccharides, disaccharides, monosaccharides, and polyols) diet. NICE recommends that

> [i]f a person's IBS symptoms persist while following general lifestyle and dietary advice, offer advice on further dietary management…[that] should include single food avoidance and exclusion diets (for example, a low FODMAP [fermentable oligosaccharides, disaccharides, monosaccharides and polyols] diet).[72]

The guideline cautions that only health care professionals with expertise in dietary management should offer dietary advice to patients with IBS. The fundamental basis for recommending a low-FODMAP diet is that bloating results from bacterial fermentation of intraluminal saccharides. Breath tests with glucose, lactulose, and other sugars are positive in IBS, suggesting small intestinal bacterial overgrowth in some patients with IBS, and that antibacterial approaches benefit some symptoms especially bloating in patients with IBS. Elsewhere,[73,74] the biological and physiological counterarguments for such a diet have been published, including the artificial circumstances in which saccharide intolerance is tested by means of sugars in a solution ingested alone by fasting patients. This analysis led to a proposal for a selective approach rather than a comprehensive exclusion of all FODMAPS. The selective approach excludes fructans, which are not digested in the human gut and are therefore potential causes of bloating in all humans, and sugars based on ethnicity (eg, lactose, given that 65% of the human population[75] has a reduced ability to digest lactose after infancy, albeit with wide regional and ethnic variations).

Moreover, systematic reviews and meta-analyses of low-FODMAP diets among patients with IBS[76] have noted that the RCTs used in the meta-analyses had a high risk of being biased, were short-duration studies (never >6 weeks), lacked definitions to substantiate claims of improvement, and lacked assessment of reintroduction of the FODMAPS during period follow-up periods. The conclusion was the symptomatic effects reported in the trials were likely to be driven primarily by a placebo response. Another meta-analysis[69] that summarized 3 trials involving 271 patients with IBS that compared a low-FODMAP diet with an alternative diet found

Table. Summary of Current Medications Approved for Treatment of Irritable Bowel Syndrome–Related Symptoms[a]

Source	Therapy class	Mechanism of action	Efficacy on SRMAs	Quality of data	Adverse events	Limitations of data
Pain						
Quartero et al,[84] 2005; Ford et al,[85]2008	Antispasmodic drugs: hyoscine, otilonium, pinaverium, cimetropium	Inhibition of muscarinic Ach receptors or block calcium ion channels, GI smooth muscle	May be effective: OR, 0.68 (95% CI, 0.57-0.71); overall NNT, 5; NNT for hyoscine, 3.5; otilonium, 4.5; cimetropium, 3; pinaverium, 3	Low	More likely with antispasmodics in a meta-analysis of 22 RCTs in 2008, particularly dry mouth, dizziness, and blurred vision	No high-quality trials, heterogeneity between studies, possible publication bias, and only a small number of RCTs assessing each individual antispasmodic
Black et al,[70] 2020; Ford et al,[85]2008; Khanna et al,[86] 2014	Peppermint oil	Blocks L-type calcium ion channels on muscle, activate TRPM8 receptors on nociceptive afferents	Effective: OR, 0.43 (95% CI, 0.32-0.59); Global: RR 2.23 (95% CI, 1.78-2.81); overall NNT, 2.5; RCT of sustained release formulation: decrease pain, bloat, urgency but not total IBS scores	Moderate	No increase in adverse events in a meta-analysis of 4 RCTs	Heterogeneity between studies; ranked first for global IBS symptoms in network meta-analysis
Black et al,[70] 2020; Ford et al,[87]2014	Antidepressants	Psychological, antinociceptive, slow (TCA) or fast (SSRI) transit effects	Effective: OR, 0.67 (95% CI, 0.58-0.77); for global: OR, 0.62 (95% CI, 0.43-0.88); NNT, 4 for abdominal pain	Moderate	More likely with antidepressants in a meta-analysis of 17 RCTs, particularly dry mouth and drowsiness	Only 3 high-quality trials, heterogeneity between studies, possible publication bias, and some atypical trials included; NNT overestimates efficacy; ranked first for abdominal pain in network meta-analysis
Diarrhea						
	Loperamide	μ-Opioid agonist inhibits secretion, transit	Unknown for IBS; effective for diarrhea	Low	Limited data	Few RCTs, with a small number of participants, not all of whom had IBS
Black et al,[88] 2020	Eluxadoline	κ-Opioid and μ-opioid receptor agonists and δ-opioid receptor antagonist	Effective for FDA composite: 100 mg: OR, 0.87 (95% CI, 0.83-0.91); 75 mg: OR, 0.89 (95% CI, 0.84-0.94). RCTs: Effective for diarrhea and composite diarrhea + pain; not pain alone	High	Serious adverse events included acute pancreatitis and sphincter of Oddi spasm, nausea, and headache more common with active therapy	Only a modest benefit over placebo in published RCTs. No benefit over placebo in terms of abdominal pain
Black et al,[88] 2020; Andresen et al,[89] 2008	5-HT_3 receptor antagonists: ondansetron, alosetron, ramosetron	Retard colonic transit and reduce visceral pain	Effective global: RR, 1.60 (95% CI, 1.49-1.72); Pain: RR, 1.30 (95% CI, 1.22-1.39); FDA composite: OR, 0.69 (95% CI, 0.60-0.80) RCTs: effective for all symptoms: diarrhea; composite diarrhea + pain; and pain alone	High	Serious adverse events with alosetron included ischemic colitis and severe constipation; ramosetron and ondansetron may be safer although constipation more common with active therapy	Fewer RCTs of ramosetron and ondansetron; ondansetron may have no benefit over placebo in terms of abdominal pain; network meta-analysis: alosetron and ramosetron the most effective for IBS-D/M
Vijayvargiya et al,[68] 2020; Camilleri et al,[90] 2015; Bajor et al,[91] 2015	Bile acid sequestrants: cholestyramine, colestipol, colesevelam	Bind intraluminal bile acids	Unknown: effective in open-label studies; ineffective in 1, single-center RCT	Low	Limited data	One RCT of colesevelam in bile acid diarrhea showed no significant effects on stool frequency and consistency or on colonic transit
Black et al,[88] 2020; Menees et al,[92] 2013	Rifaximin	Nonabsorbable antibiotic	Effective 2012 SMRAs: Global: OR, 1.57 (95% CI, 1.22-2.01); Bloating: OR, 1.55 (95% CI, 1.23-1.96); 2020 SRMA: FDA composite: OR, 0.92 (95% CI, 0.86-0.98); Global OR: 0.91 (95% CI, 0.77-1.07)	Moderate	No increase in adverse events in a meta-analysis of 5 RCTs	Only a modest benefit over placebo in published RCTs; efficacy inferior to alosetron and ramosetron on network meta-analysis
Constipation						
Chapman, et al,[93] 2013	PEG 3350	Osmotic secretion	Effective: improves SBMs, complete SBMs, consistency straining but not pain, bloating or incomplete evacuation	Moderate	Diarrhea and abdominal pain	Few trials in IBS-C; 4-wk trial data
Drossman et al,[94] 2009; Chey et al,[95] 2012	Lubiprostone	Chloride channel activation and with *CFTR* stimulate $chlorine^-$ secretion; inhibitor of NHE3	Effective: pooled analysis from 2 RCTs, response rates (>moderate relief of global symptoms for 2 of 3-mo therapy): 17.9% lubiprostone vs 10.1% placebo	Moderate	Nausea more common with active therapy, occurring in 8% of patients	Only a modest benefit over placebo in published RCTs; 8 μg 2/d efficacious in 52 week RCT trial in IBS-C

(continued)

Table. Summary of Current Medications Approved for Treatment of Irritable Bowel Syndrome–Related Symptoms[a] (continued)

Source	Therapy class	Mechanism of action	Efficacy on SRMAs	Quality of data	Adverse events	Limitations of data
Videlock et al,[96] 2013; Luthra et al,[97] 2019	Linaclotide	Guanylate cyclase C activator, stimulate chlorine$^-$ and water secretion via *CFTR*; visceral analgesia	Effective: adequate relief IBS: RR, 1.95 (95% CI, 1.3-2.9); Abdominal pain: RR, 1.58 (95% CI, 1.02-2.46); 12-wks Rx chronic constipation: RR, 0.86 (95% CI, 0.82-0.91) for 290 µg; RR, 0.85 (95% CI, 0.85-0.93) for 145 µg; RR, 0.90 (95% CI, 0.84-0.96) for 72 µg	High	Diarrhea more common with active therapy, occurring in 20% of patients (definition of diarrhea different from that used in plecanatide trials)	None
Brenner et al,[98] 2018; Barish et al,[99] 2018	Plecanatide		Effective: for 12-wk prescription chronic constipation: RR, 0.91 (95% CI, 0.86-0.95) for 3 mg; RR 0.91 (95% CI, 0.86-0.96) for 6 mg	High	Diarrhea more common with active therapy, occurring in ≈ 6% of patients	None; long-term efficacy and safety reported in 2370 patient exposures for up to 72 wk
Chey et al,[100] 2020	Tenapanor	NHE3 inhibitor stimulates sodium$^+$, water secretion	Effective at 50 mg 2/d; NNT, 7-9 for complete SBM and combined complete SBM ≥30% pain reduction; 11 for abdominal pain reduction >30% alone	Moderate	Diarrhea more common with active therapy, occurring in 12% of patients	None
Luthra et al,[97] 2019; Evans et al,[101] 2007; Black et al,[102] 2020	5-HT_4 receptor agonists: tegaserod, prucalopride	Stimulate colonic motility and transit	Effective for 12-wk prescription chronic constipation: RR, 0.93 (95% CI, 0.88-0.98) for 2 mg 2/d; RR, 0.88 (0.84-0.93) for 6 mg 2/d; in 2019 SRMA, tegaserod 6 mg 2/d showed RR, 0.85 (95% CI, 0.80-0.91)	High	Diarrhea, cramping, and cardiovascular adverse events with older generation drugs in this class	Data available for tegaserod IBS-C, not for new generation drugs in this class: prucalopride, naronapride, velusetrag; tegaserod approved for younger women with IBS-C
Nakajima et al,[103] 2018	IBAT inhibitor: elobixibat	Increases colonic bile acid levels to induce secretion and motility	Effective for chronic constipation, 5 mg/d; RR, 0.90 (95%, CI, 0.83-0.98); 10 mg/d; RR, 0.96 (95% CI, 0.89-1.04)	Moderate	Diarrhea, cramping	Within chronic constipation group, patients with positive IBS-C have similar response

Abbreviations: Ach, acetylcholine; CFTR, transmembrane conductance regulator; FDA, US Food and Drug Administration; GI, gastrointestinal; 5-HT_3, serotonin type 3; IBAT, ileal bile acid transporter; IBS, irritable bowel syndrome; IBS-C, constipation; IBS-D, diarrhea, IBS-M, mixed symptoms; NHE3, sodium-hydrogen exchanger 3; NNT, number needed to treat; OR, odds ratio; PEG 3350, polyethylene glycol 3350; RCT, randomized clinical trial; RR, relative risk; Rx, prescription; SSRI, selective serotonin reuptake inhibitor; SBM, spontaneous bowel movement; SRMA, systematic review and meta-analysis; TCA, tricyclic antidepressant; TRPM8, transient receptor potential cation channel subfamily melastatin member 8.

[a] Adapted from Camilleri et al.[104]

no statistically significant benefit of a the low-FODMAP diet (RR, 0.82; 95% CI, 0.66-1.02).

Psychotherapy

Overall, evidence so far does not show psychological therapies to be effective in relieving symptoms of IBS. One systematic review and meta-analysis[77] reported that 52.2% of 1407 patients in the psychotherapy group did not experience IBS relief nor did 76.2% of 1282 patients in the control groups (RR, 0.69; 95% CI, 0.62-0.76). Data pooled from at least 2 RCTs reported that cognitive behavioral therapy (CBT), relaxation therapy, multicomponent psychological therapy, hypnotherapy, and dynamic psychotherapy were all beneficial. However, the study reported methodological concerns due to significant heterogeneity between studies and significant funnel plot asymmetry, suggesting publication bias and problems related to trial design, including lack of blinding. Nevertheless, some studies reported[78-81] that web-based or telephone-based delivery of CBT and patient-centered short-term CBT were effective compared with usual treatment, so these should be considered where available particularly for the patients with psychological comorbidity.

Alternative Medicine

Alternative medicine may have some effect in treating patients with IBS. In an systematic review and meta-analysis[82] that included 21 RCTs involving 1834 patients with IBS-D, acupuncture combined with Chinese herbal medicine compared with Western medicine such as the calcium channel blocker pinaverium bromide demonstrated favorable improvements compared with the control group (RR, 1.29; 95% CI, 1.24-1.35) including effects on abdominal pain, distension, and diarrhea. Of the 929 patients, 93.5% responded to the active treatment, whereas 72.3% of 904 responded to the control treatment. An earlier systematic review and meta-analysis[83] found no benefit relative to sham-controlled acupuncture.

Pharmacotherapy

The **Table**[68,70,84-104] provides a summary of the mechanisms of action, efficacy, adverse effects, and other comments, for the 3 classes of therapy for pain, diarrhea, and constipation. In summary, the mainstays of treatment are antispasmodic and neuromodulator agents (antidepressants, typically using tricyclic agents to treat diarrhea and selective serotonin reuptake inhibitors to treat constipation) for pain, and loperamide (first-line) and serotonin type 3

(5-HT_3) antagonists (indicated for women with severe IBS-D lasting ≥6 months and for whom conventional therapy was inadequate). A network meta-analysis[88] showed that 5-HT_3 antagonists, particularly alosetron and ramosetron, are the most effective agents for the treatment of functional diarrhea and IBS-D.

Several approaches are available to treat constipation, including osmotic laxatives, chloride secretagogues, ion channel blockers, ileal bile acid transporter inhibition, and prokinetic agents (Table). Given that the therapeutic trials involving patients with chronic constipation never differentiated patients with normal or slow colonic transit, it is not possible to select one class over another when information on colonic transit is available. In a network meta-analysis[97] of treatments for constipation disorders, diphenylmethane (bisacodyl) was most effective at 4 weeks for chronic constipation, but it was not tested over the 12 weeks of the trial's duration; thus, over a period of 12 weeks of treatment, the network meta-analysis on chronic constipation suggests greatest efficacy with prucalopride.

Microbial Manipulation

Other than the efficacy documented with use of the unabsorbed antibiotic for IBS-D, rifaximin,[88,92] as detailed in the Table and in a meta-analysis,[105] the potential approaches that manipulate intestinal microbes are prebiotics, probiotics, synbiotics, and fecal microbial transplant.

A few, small studies support the potential utility of synbiotics and prebiotics. For example, Flortec, a symbiotic containing *Lactobacillus paracasei* B21060 as well as prebiotics, xylooligosaccharides, glutamine, and arabinogalactone, improved pain and well-being compared with a preparation of the same 3 prebiotics in patients with IBS-D.[106] Gelsectan is a combination prebiotic containing xyloglucan, pea protein and tannins from grape seed extract, and xylooligosaccharides. It was efficacious in a 4-week, placebo-controlled, randomized, crossover trial involving patients with IBS-D.[107]

The probiotic[108] *Bifidobacterium longum* NCC3001 reduces depression scores, improves quality of life, and alters brain activity by reducing flow in multiple brain areas, including amygdala and frontolimbic regions that are associated with negative emotional stimuli in patients with IBS.

A systematic review and meta-analysis[105] of the efficacy of prebiotics, probiotics, synbiotics, and antibiotics in IBS concluded that particular combinations of probiotics or specific species and strains appeared beneficial for global IBS symptoms and abdominal pain but that it was not possible to draw definitive conclusions about their efficacy.

Although a systematic review of gut microbiota showed no consistent abnormalities in IBS or different subgroups,[109] there have been many studies of the potential effect of fecal microbiota transplant. A systematic review and meta-analysis involving 267 patients showed no significant benefit whether administered by capsule, colonoscopy, or nasojejunal tube with an overall nonsignificant RR of 0.98 (95% CI, 0.58-1.66); thus, fecal microbiota transplant was nearly equivalent to placebo: 50% of 158 patients in the transplant group vs 51.4% of 109 patients in the placebo group did not benefit from the treatment.[110] Most recently, there has been considerable interest in the results of a study using stool from a superdonor. The study compared placebo with 30-g and 60-g doses that were delivered via upper gastrointestinal endoscopy. Treatment efficacy was established as a reduction in IBS symptom severity scores of 50 points on a 500-point scale.[111] However, more than 50% of those who received the active treatment had moderate severity with scores higher than 175, and more than 25% had severe symptoms with scores higher than 300. Thus, although it appears that fecal microbiota transplant from the super donor was beneficial in the treatment of IBS compared with placebo, 75% of the treated patients still had moderate or severe IBS symptom severity. Moreover, around 20% of the patients in the fecal microbiota transplant group reported adverse effects of abdominal pain, cramping or tenderness, diarrhea, or constipation compared with only 2% of patients in the placebo group. It is also important to recognize risks associated with fecal microbiota transplant. Thus, 2 immunosuppressed patients developed bacteremia with an antibiotic-resistant *Escherichia coli* strain, one of whom died, after administration of fecal microbiota transplant capsules derived from same donor.[112] On March 13, 2020, the US Food and Drug Administration issued a warning of potential risk of serious infections due to fecal microbiota transplant caused by enteropathogenic or Shigatoxin–producing *E coli* (STEC) that have occurred following investigational use of a fecal microbiota transplant product supplied by a stool bank (from prescreened donors).[113]

Conclusions

Advances in the identification of specific dysfunctions as causes of individual symptoms in the "IBS spectrum" leads to the potential to enhance the diagnosis and management of the majority of patients in whom first-line therapies of IBS and management of comorbid psychological disorders are insufficient.

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Submissions: We encourage authors to submit papers for consideration as a Review. Please contact Edward Livingston, MD, at Edward.livingston@jamanetwork.org or Mary McGrae McDermott, MD, at mdm608@northwestern.edu.

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