Diagnosis and management of IBS

Sarah Khan and Lin Chang

Abstract | IBS is a common gastrointestinal condition characterized by chronic or recurrent abdominal pain associated with altered bowel habits. IBS is considered a functional bowel disorder (that is, not defined by structural or biochemical abnormalities) and is diagnosed using symptom-based criteria. Limited and judicious use of diagnostic testing is recommended, particularly in patients with typical symptoms of IBS without alarm signs and symptoms. Management of IBS is based on a multifactorial approach and includes establishment of an effective patient–provider relationship, education, reassurance, dietary alterations, pharmacotherapy, behavioral and psychological treatment. Patient-centered care is recommended, in which management is focused on the patient's most bothersome and impactful symptoms, their preferences and previous experiences with treatment, and addressing factors associated with the onset and exacerbation of symptoms. Pharmacotherapy is typically targeted against the predominant symptom. This Review discusses the current evidence-based recommendations for the diagnosis and management of IBS. An improved understanding of the recommended diagnostic and therapeutic approaches for IBS will lead to greater patient satisfaction, as well as reduced health-care costs.

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Introduction

IBS is estimated to affect 7–15% of the general population in the USA.[1,2] The prevalence of IBS is reported to be 2.5–22.0% in the UK, 4.4–13.6% in Spain, and less than 10% in Italy, France, Denmark and Sweden.[3–11] The prevalence of IBS in Asian countries including China, Japan, Korea, Singapore and India ranges from 6 to 11.5%.[12] IBS is frequently categorized into a subtype by predominant bowel habit: diarrhea-predominant IBS (IBS-D); constipation-predominant IBS (IBS-C); or mixed pattern IBS (IBS-M) (Box 1). Prior to the Rome III subclassification of bowel habit predominance in IBS, IBS with alternating bowel habits (IBS-A) was used to describe patients with mixed pattern IBS. The Rome III subclassification now uses the term IBS-M to refer to these patients and the term IBS-A for patients who transition over time between the bowel habit subtypes.[1] The prevalence of each subtype varies in studies; reports of equal prevalence exist,[13] but others claim IBS-D[14] or IBS-M[15] to be the most common subtypes. IBS is more prevalent in women, although estimates of a 2.0–2.5:1 ratio of women to men in clinic settings is higher than that reported in the general population.[16] Young, adult patients are more commonly diagnosed with IBS than those over the age of 50 years, with the first presentation to a physician often being between the ages of 30 and 50 years.[2] Lack of employment and marital status (unmarried) have been reported to be associated with IBS.[14]

A large proportion of individuals with IBS (33–90%) do not seek health care for their symptoms.[17] Up to 50% of IBS cases in the UK are thought to be undiagnosed.[17] Predictors for health-care seeking for IBS include severe symptoms (particularly pain) and psychological variables (for example, anxiety, depression, abuse, illness behavior, somatic attribution and health concerns).[18,19]

Comorbid symptoms or disorders are common in patients with IBS, particularly those with severe symptoms and in those attending referral practices. Psychiatric comorbidity (major depression, anxiety and

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Center for Neurobiology of Stress, Division of Digestive Diseases, David Geffen School of Medicine at UCLA, 10833 Le Conte Avenue, CHS 47-122, Los Angeles, CA 90095-7378, USA (**S. Khan, L. Chang**).

Correspondence to: L. Chang
linchang@ucla.edu

Key points

- IBS can be confidently diagnosed with symptom-based criteria in the absence of alarm signs
- Management of IBS involves an integrative approach, including establishment of an effective patient–provider relationship, education, reassurance, dietary alterations, pharmacotherapy aimed at the most bothersome symptoms, behavioral and psychological treatment
- Fiber, laxatives, a chloride channel activator and, rarely, 5-HT_4 agonists are used to treat constipation-predominant symptoms
- Antidiarrheal agents, antibiotics, tricyclic antidepressants and, in severe cases, a 5-HT_3 antagonist are used to treat diarrhea-predominant symptoms
- Dietary measures, probiotics and antibiotics may be efficacious for reducing bloating and gas; antidepressants and anticholinergics can help relieve abdominal pain
- Effective psychological and behavioral treatment interventions for IBS include cognitive behavioral therapy, hypnosis, psychotherapy and stress management

Box 1 | Bowel habit subtype classifications*[1]

IBS with constipation (IBS-C)
- Hard or lumpy stools‡ ≥25% of bowel movements
- Loose (mushy) or watery stools§ <25% of bowel movements‖

IBS with diarrhea (IBS-D)
- Loose (mushy) or watery stools§ ≥25% of bowel movements
- Hard or lumpy stools‡ <25% of bowel movements‖

Mixed IBS (IBS-M)[d]
- Hard or lumpy stools‡ ≥25% of bowel movements
- Loose (mushy) or watery stools§ ≥25% of bowel movements‖

Unsubtyped IBS
- Insufficient abnormality of stool consistency to meet criteria for IBS-C, D, or M¶

*The following subclasssification may be used to subtype patients according to bowel habit for research or clinical trials. ‡Bristol Stool Form Scale 1–2 (separate hard lumps like nuts [difficult to pass] or sausage shaped but lumpy). §Bristol Stool Form Scale 6–7 (fluffy pieces with ragged edges, a mushy stool or watery, no solid pieces, entirely liquid). ‖In the absence of use of antidiarrheals or laxatives. ¶Although IBS-M classification is a useful way of describing this subtype at presentation, bowel habits often vary over time, and the term IBS with alternating bowel habits (IBS-A) is proposed for such cases.

somatoform disorders) in patients with IBS has been estimated to be about 48–60% in those attending gastroenterology clinics[20] and up to 70% in those attending tertiary care referral centers.[21] Nonpsychiatric, nongastrointestinal disorders that coexist with IBS include fibromyalgia,[22] chronic fatigue syndrome[23] and chronic pelvic pain.[24] However, the prevalence of comorbid symptoms and disorders are not the same for all patients. These symptoms and disorders tend to exist on a continuum depending on the health-care setting within which the patients are seen (for example, general population, primary care or referral settings) or the severity of the underlying condition.[25]

The burden of illness of IBS is significant. Patients with IBS have decreased health-related quality of life (HRQOL) scores compared with healthy controls and patients with GERD, diabetes and end-stage renal disease.[26,27] In a natural history study conducted over 1 year in Canada, overall disease-specific HRQOL, measured by the validated IBS-QOL questionnaire,[28] was decreased; food avoidance and health worry domains were the most serious concerns for patients.[29] HRQOL in IBS is related to abdominal pain, symptom flares, extraintestinal symptoms and disease-related concerns.[26,30] Interestingly, other gastrointestinal symptoms and demographic factors (age, gender, marital status) do not significantly predict HRQOL in IBS.[31] Patient-assessed disease severity in IBS was found to be related to, yet distinct from, generic HRQOL.[32] IBS severity was predicted by abdominal pain, bloating, straining, urgency, myalgias and disease-related concern.[31]

There is also a great economic burden associated with IBS owing to substantial direct health-care costs and indirect costs (related to impaired work productivity).[33] In a systematic review of studies conducted in the USA and UK, total direct costs per patient per year ranged from US$348 to $8,750, and indirect costs per patient per year ranged from $355 to $3,344 in 2002.[34] In addition, the average number of days off work because of IBS per year was between 8.5 to 21.6.[34] Dean *et al.*[35] found that patients with IBS exhibited 20% more impairment in work productivity compared with their fellow employees without IBS. Patients with IBS use more health-care services than the general population, even for non-gastrointestinal symptoms.[36,37] They also undergo more surgical procedures—including cholecystectomy, appendectomy, hysterectomy and back surgery—compared with individuals without IBS.[38]

Although the pathophysiology of IBS is not completely understood, evidence supports the hypothesis that it is multifactorial. Studies have reported that genetic factors, chronic stress and enteric infections can predispose individuals to developing IBS. Dysregulations in brain–gut interactions are thought to result in alterations in autonomic response, immune function, gut motility and visceral perception that manifest as symptoms of IBS.[39] Postinfectious IBS (PI-IBS) has provided a model for understanding the pathophysiologic mechanisms associated with IBS. Patient characteristics associated with a predisposition to developing PI-IBS are female gender, young age (19–29 years), severe gastrointestinal infection and a history of chronic stressful life events.[40–42] Gwee *et al.* found that following infection, patients with PI-IBS demonstrated rapid colonic transit, enhanced rectal sensitivity and increased rectal mucosal inflammatory markers after 3 months compared with healthy controls and infected patients who did not develop IBS.[43,44] Thus, acute colonic inflammation led to alterations in visceral perception and motility that persisted after the infection had cleared. The combination of central and peripheral factors in the development of PI-IBS lends support for a biopsychosocial model in IBS.

This Review provides clinicians with a current and predominantly evidence-based review of the diagnosis and management of IBS. Two systematic reviews, by the

American College of Gastroenterology (ACG)[45] and the British Society of Gastroenterology (BSG),[17] offer guidelines on the management of IBS. Their findings and summaries have been considered in this Review, with the addition of more recently published studies. Also, some treatment trials that were not included in the ACG review, which primarily evaluated studies in which global IBS symptoms or abdominal pain was the main outcome measure, are incorporated into this Review. A better understanding of recommended diagnostic and therapeutic approaches can lead to increased patient satisfaction as well as reduced health-care costs.

Diagnosis of IBS

Clinical symptoms

The hallmark symptom of IBS is abdominal pain. It is the key symptom that is associated with HRQOL,[30] illness severity[46] and health-care utilization.[47] The diagnosis of IBS is based on the association of abdominal pain with altered bowel habits, that is, diarrhea and/or constipation. Pain related to IBS is typically worse with eating, associated with a change in stool consistency, and improved by bowel movements. Between 20% and 45% of the general adult population believe that they suffer from adverse reactions to food, and up to 70% of patients with IBS attribute their symptoms to adverse food reactions.[48,49] Pain that is continuous in nature, unrelated to a change in bowel habits, and not explained by organic disease is more likely to be due to functional abdominal pain than IBS (in which pain has more of an intermittent nature).[50] Given that IBS is typically painful, painless diarrhea or constipation without evidence of organic disease is more likely to be functional diarrhea or functional constipation, respectively.[1]

Other commonly reported symptoms in IBS are hard or loose stools, urgency, straining, bloating, a sensation of incomplete evacuation and mucus in the stool. Bloating is reported in up to 96% of patients with IBS[1] and can be associated with visible abdominal distension. Patients with IBS also have a greater prevalence of nongastrointestinal symptoms than controls, including headache, fatigue, myalgias, dyspareunia, urinary frequency or other urinary symptoms, dizziness and psychological symptoms. These extraintestinal symptoms are more common in patients with severe illness and may be due to overlapping conditions such as fibromyalgia, chronic pelvic pain disorders and chronic fatigue syndrome.[23]

The association of IBS symptoms with menstruation and other gynecological features (for example, dyspareunia) may make the diagnosis more complex[51] and can lead to unnecessary surgical intervention (for example, laparoscopies to investigate symptoms or surgical treatment for suspected organic disease).[38] Heitkemper and colleagues found that the severity of premenstrual symptoms was higher in women with IBS, and dysmenorrhea was twice as common in women with IBS as control patients. IBS symptoms, particularly bloating, are increased in women just prior to the onset of menses.[51]

Box 2 | Rome III criteria for IBS

Recurrent abdominal pain or discomfort* at least 3 days per month in the last 3 months‡ associated with 2 or more of the following:

1. Improvement with defecation
2. Onset associated with a change in frequency of stool
3. Onset associated with a change in form (appearance) of stool

*Discomfort means an uncomfortable sensation not described as pain. In pathophysiology research and clinical trials, a pain and/or discomfort frequency of at least 2 days a week during screening evaluation is necessary for subject eligibility. ‡Criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis.

Symptom-based diagnostic criteria

There have been several symptom-based criteria employed for the diagnosis of IBS, primarily for use in clinical research studies. In general, these criteria include the presence of chronic or recurrent abdominal pain or discomfort in the presence of altered bowel habit. The Manning diagnostic criteria were first introduced in 1978 and identified abdominal pain relieved by defecation, looser stools and more frequent stools at onset of pain, passage of mucus, incomplete emptying of rectum and abdominal distension as key features of IBS.[52] However, there was no mention of symptom duration in these criteria. The Kruis criteria, developed in 1984, suggested a 2-year time duration and inclusion of negative physical examination findings and blood testing (for example, erythrocyte sedimentation rate [ESR], complete blood count) in the diagnostic process.[53] In 1990, the Rome criteria were developed and reduced unnecessary testing by removing the requirement of negative blood tests and physical examination findings. These criteria were originally developed for research purposes, that is, a relatively homogenous population was defined in order to study pathophysiology and treatment responses. The most recent iteration of the Rome criteria, the Rome III criteria for IBS and its subtypes, was introduced in 2006 (Boxes 1 and 2).[1] These diagnostic criteria are currently used in clinical research and to a lesser extent in clinical practice.

Two systematic reviews have assessed the accuracy of gastrointestinal symptoms and diagnostic criteria in discriminating IBS from organic disease.[54,55] Ford *et al.*[54] found that lower abdominal pain had a high sensitivity (90%) but very low specificity (32%) for the diagnosis of IBS and thus had the best negative likelihood ratio. The three other symptoms relating to abdominal pain (passage of looser stools at the onset of abdominal pain, more frequent stools at the onset of abdominal pain, and abdominal pain relieved by defecation) had better specificity (73%, 72%, 66%, respectively) but lower sensitivity (58%, 53%, 60%, respectively) and provided the best positive likelihood ratios for the diagnosis of IBS. Thus, the absence of abdominal pain reduces the likelihood that IBS is the cause of the lower gastrointestinal symptoms. This study also concluded that the accuracies of the

Manning and Kruis criteria were modest.[54] Jellema and colleagues[55] found that the diagnostic performance of the Manning and Kruis criteria in excluding organic disease had a sensitivity of only 34–46% but a high specificity of 82–91%.

Validation of the Rome criteria has been performed for Rome I but less so for the subsequent iterations. A study that assessed the accuracy of the Rome I criteria for diagnosing IBS found that it had a sensitivity of 85% and specificity of 71% with a significant odds ratio (OR) of 13.3 (95% CI 8.9–20.0), a positive predictive value of 86% and a negative predictive value of 69%.[56] Vanner and colleagues[57] performed retrospective and prospective analyses to assess the predictive value of the Rome I and II criteria without the presence of alarm signs and symptoms. The retrospective chart review of 98 gastroenterology clinic patients with one or more Rome criteria found that the criteria combined with the absence of alarm symptoms had a sensitivity of 65%, specificity of 100%, positive predictive value of 100% and a negative predictive value of 76%.[57] In their prospective study of 95 gastroenterology clinic patients who met Rome criteria, did not have alarm signs and symptoms, and underwent diagnostic evaluation, the positive predictive value was 98%. A systematic review conducted by Jellema *et al.*[55] found that the diagnostic performance of the Rome II criteria for excluding organic disease demonstrated sensitivities ranging from 31% to 65% and specificities ranging from 30% to 100%.

Alarm signs and symptoms

Alarm features are signs and symptoms that should immediately prompt the investigator to consider an alternative diagnosis, such as IBD or colon cancer. These 'red flags' include new onset of symptoms at 50 years or older, unintentional weight loss, nocturnal diarrhea, anemia, bloody stools, and family history of colon cancer, celiac disease or IBD. A study from Australia in 2004 evaluated the diagnostic yield of alarm symptoms for distinguishing organic disease from Rome II positive IBS and functional dyspepsia.[58] Logistic regression models found age (50 years at symptom onset; OR 2.65 [95% CI 1.4–5.0]) and blood on the toilet paper (OR 2.7 [95% CI 1.4–5.1]) to be alarm features that significantly discriminated organic lower gastrointestinal disease from IBS. Patients with IBS reported more upper and lower abdominal pain, more pain radiating outside the abdomen, duration of pain more than 2 years, pain on six or more occasions in the past year and pain episodes lasting more than 30 min in duration.[58] Nocturnal abdominal pain did not discriminate between IBS and organic disease.[58] In another review of the diagnostic utility of alarm features for colorectal cancer, the pooled sensitivity of alarm features was poor (5–64%); however, dark red blood per rectum and an abdominal mass had a specificity of >95%, which suggests that the presence of either feature is indicative of colon cancer.[59] Studies suggest that family history of celiac disease,[60] IBD[61] and colorectal cancer[62] are more indicative of a diagnosis of organic disease than IBS.

Diagnostic testing

The differential diagnosis of IBS symptoms is broad (Box 3), which can lead to multiple, but often unnecessary, diagnostic tests. Routine diagnostic testing is more likely to be performed when clinicians believe IBS to be a diagnosis of exclusion. In a study by Spiegel *et al.*,[63] health-care providers who believed that IBS was a diagnosis of exclusion ordered on average 1.6 times more tests and spent US$364 more evaluating a patient with typical IBS symptoms than those who did not believe that IBS is a diagnosis of exclusion. The ACG IBS Task Force recommend that routine diagnostic testing should not be performed for patients with typical IBS symptoms without alarm features (Table 1).[45] With the exception of tests for lactose intolerance and celiac disease, the prevalence of abnormalities of other diagnostic tests was not significantly different between patients with IBS with no alarm features and healthy controls. However, the BSG guidelines recommend ordering a full blood count in patients who are older at first presentation (>50 years), and full blood count, ESR and C-reactive protein in patients with recent onset of IBS-D.[17]

In some patients with IBS symptoms, diagnostic testing is warranted even in the absence of alarm signs. A systematic review and meta-analysis ($n = 4,204$) was conducted to estimate the prevalence of celiac disease in patients who met Rome criteria.[64] The investigators found the prevalence of biopsy-proven celiac disease to be increased fourfold in individuals with IBS symptoms compared with matched healthy controls.[64] The ORs between IBS-C, IBS-D and IBS-A subtypes were not significant. Testing for celiac disease in patients with IBS-D versus empiric therapy for IBS-D has been shown to be cost-effective if the prevalence of celiac disease in the population is greater than 1%.[65,66] This approach is advocated in the BSG guidelines.[17,45] The ACG IBS Task Force recommends routine serologic screening for celiac disease in patients with IBS-D and IBS-M. The prevalence of celiac disease in patients with IBS-C has not been well studied.[45]

Colonoscopy, in general, is not recommended in patients with IBS who do not have alarm signs. However, colonoscopy should be performed in patients with IBS who have alarm features to rule out organic disease, and in those over the age of 50 years as routine screening.[45] A prospective study by Chey *et al.*,[67] published in 2010, compared the prevalence of structural colonic lesions in patients with non-constipating IBS without alarm features and healthy controls undergoing colon cancer screening or surveillance because of a history of adenomatous polyps (Table 2). Compared with the control patients, patients with IBS were significantly younger (mean age 41.1 ± 12.9 years 53.8 ± 7.7 years) and more likely to be female (69% versus 41%). The common lesions found in patients with IBS were hemorrhoids (18.2%), polyps (14.6%) and diverticulosis (8.8%), although none of these findings would explain their IBS symptoms. However, the IBS group had a lower prevalence of adenomas (7.7% versus 26.1%) and diverticulosis (8.8% versus 21.3%), compared with

controls but a higher prevalence of mucosal erythema and ulceration (4.9% versus 1.8%). The findings of this study support the ACG IBS Task Force recommendation to not perform colonic imaging in individuals under the age of 50 years with typical IBS symptoms and no alarm features.[45] However, in the study by Chey *et al.*[67] random colonic biopsies were performed in patients with IBS-D and IBS-M, and demonstrated evidence of microscopic colitis in 2.3% of patients >45 years of age and nonspecific inflammation in 1.4% of the patients with IBS. Only the patients with IBS-D were found to have microscopic colitis. The ACG IBS Task Force recommend that when colonoscopy is performed in patients with IBS-D, random biopsy samples should be taken to rule out microscopic colitis.[45] Of note, most of these studies were conducted at tertiary referral centers and therefore the prevalence of microscopic colitis and celiac disease in these patients may not reflect the prevalence in the general population. The BSG guidelines recommend colonoscopy in patients over the age of 50 who have a change in bowel habit; however, the guidelines do not explicitly recommend colonic biopsies in patients with IBS-D to rule out microscopic colitis, although this association is acknowledged.[17]

The reported prevalence of lactose maldigestion in patients with IBS is estimated to be 35% and is more prevalent than in controls (38% versus 26%, OR 2.57, 95% CI 1.27–5.22).[45] In addition, as patients with IBS have enhanced visceral perception and altered colonic motility, the clinical symptoms of lactose intolerance may be higher in patients with IBS than in healthy controls. The ACG IBS Task Force recommend ordering lactose breath testing only if suspicion is still high after a dietary exclusion trial.[45]

Small intestinal bacterial overgrowth (SIBO) is a postulated pathophysiologic mechanism of IBS.[68] The issue of whether to conduct breath tests for SIBO remains inconclusive owing to the lack of a gold standard test for SIBO.[69] Jejunal aspiration to detect SIBO is limited due to the fact that most of the proximal small bowel bacteria cannot be cultured. Controversy remains concerning the value of glucose and lactose hydrogen breath tests, which are used to diagnose SIBO, in discriminating patients with IBS from healthy individuals. Owing to disparities in the sensitivities and specificities of these two types of breath test, in patients with IBS the prevalence of a positive lactulose breath test is 65% and a positive glucose breath test is 36%.[45] Posserud *et al.*[70] performed jejunal aspiration for bacterial cultures in 164 patients with IBS and 20 healthy controls. Only 4% of patients in each group had a bacterial count of $>10^5$ colony-forming unit (cfu)/ml, which is traditionally considered indicative of SIBO. A subset of the patients with IBS and all of the controls with $<10^5$ cfu/ml underwent a lactulose and/or glucose breath test; comparable proportions of both groups had positive breath tests, which varied depending on the diagnostic criteria used for the breath test results. A meta-analysis found the sensitivity and specificity of breath testing in distinguishing patients with IBS from healthy controls to be 72.2% and 66.0%, respectively, for

Box 3 | Differential diagnosis of IBS symptoms

Infection
- Parasitic
- HIV and associated infections
- Viral gastroenteritis
- Amoebic infections
- Giardiasis

Food and diet
- Lactose intolerance
- Fructose intolerance
- Fatty foods
- Alcohol
- Caffeine
- Food allergy
- Artificial sweeteners

Other functional gastrointestinal disorders
- Functional abdominal pain
- Functional dyspepsia
- Functional diarrhea/constipation

IBD or other organic gastrointestinal disorders
- Crohn's disease
- Ulcerative colitis
- Microscopic/collagenous colitis
- Celiac disease
- Ischemic colitis
- Bowel obstruction
- Pancreatic insufficiency
- Bile acid related disorders
- Postgastrectomy disorders

Gynecologic conditions
- Endometriosis
- Dysmenorrhea
- Ovarian cancer

Neurologic conditions
- Spinal cord pathology
- Multiple sclerosis
- Parkinson's disease

Endocrine or metabolic disorders
- Thyroid disorder
- Diabetes mellitus
- Pancreatic endocrine tumors
- Hypercalcemia
- Acute intermittent porphyria

Psychiatric disorders
- Panic disorder
- Somatization
- Anxiety disorder

Gastrointestinal symptoms related to medications
- Antibiotics
- Chemotherapy agents
- Opiates
- Antidepressants
- NSAIDs
- PPIs
- Antihypertensive agents (e.g. Ca^+-channel blockers)

Table 1 | ACG IBS Task Force recommendations for diagnostic testing[45]

Diagnostic test	Recommendations
Routine blood tests (complete blood count, chemistries, thyroid function, stool ova/parasites)	Should only be performed if alarm symptoms are present
Celiac disease serology	Recommended in IBS-M and IBS-D
Abdominal radiological imaging	Should only be performed if alarm symptoms are present
Colonoscopy	Recommended if alarm symptoms/signs are present to rule out organic disease Recommended in patients aged ≥50 years for routine screening Not recommended if no alarm symptoms in patients aged <50 years with typical IBS symptoms Colonic biopsies are recommended if performing a colonoscopy in IBS-D to rule out microscopic colitis
Breath testing to rule out lactose intolerance	Only recommended if clinical suspicion is high and exclusion diet has failed
Breath testing for SIBO	Not routinely recommended due to insufficient data

Abbreviations: IBS-D, diarrhea-predominant IBS; IBS-M, mixed pattern IBS; SIBO, small intestinal bacterial overgrowth.

the lactulose breath test and 15.7% and 97.0%, respectively, for the glucose breath test.[71] The ACG IBS Task Force does not recommend breath testing for SIBO in patients with IBS owing to insufficient data.[45] The BSG guidelines recommend testing for SIBO only in cases of severe diarrhea, especially when it causes awakening during sleep.[17]

Extensive unnecessary testing could be avoided if a biomarker that was sensitive, specific and widely available for the efficient diagnosis of IBS in the outpatient setting existed. Lembo *et al.*[72] evaluated a panel of 10 biomarkers. The biomarkers were selected (after a comprehensive search and identification of 600 relevant pathways) based on the accuracy of differentiating IBS from non-IBS samples. Serum samples were collected from healthy controls ($n = 235$), patients with IBS ($n = 876$), IBD ($n = 398$), celiac disease ($n = 57$) and other functional gastrointestinal disorders ($n = 155$) from expert and community centers across the USA. The biomarker panel used was found to have a sensitivity of 50% and a specificity of 88% for differentiating between IBS and non-IBS individuals. The positive predictive value was 81% and the negative predictive value was 64% for a population of patients with a 50% prevalence of IBS. Although this is a novel approach, further work is needed to develop a biomarker panel with greater accuracy and with a defined target patient population before it should be used routinely in clinical practice.

Management of IBS

The management of IBS is multifaceted and often driven by illness severity, predominant symptoms, and patient and practitioner preferences (Figure 1). A graduated treatment approach with a palliative coping strategy has been suggested for the management of patients with IBS.[73] For mild symptoms, education, reassurance and dietary adjustment can suffice. For moderate symptoms, identification and modification of exacerbating factors, psychotherapeutic and/or behavioral techniques and pharmacological therapy aimed at the predominant symptoms are recommended. For severe symptoms, physician-based behavior modification and psychopharmacologic agents are useful. For intractable symptoms, referral to a pain treatment center may be needed, although this should be avoided if narcotic administration is the predominant form of treatment, as this is not a useful form of treatment for chronic functional abdominal pain and can lead to the development of narcotic bowel syndrome.

General measures

The therapeutic potential of an effective patient–provider relationship is important in the management of IBS. Positive patient–physician relationships are associated with improved health status and efficiency of patient care.[74] The impact of IBS symptoms on patients is associated with feelings of shame, fearfulness and embarrassment, which patients perceive to be poorly understood by physicians, as well as by family and friends.[75] The focus of the patient interview should be to obtain a clear and concise medical history, to develop a therapeutic relationship (that is, an alliance between the physician and the patient that effects a beneficial change), and to communicate a treatment plan with an interview style that is flexible and patient-centered. A survey of patients with IBS revealed that the most desirable qualities and behaviors of a physician were delivering comprehensive information, referring to a source for additional information, answering questions, listening, providing information about IBS studies and medications, and providing support and hope.[76]

Diet

70% of patients with IBS believe that diet has a role in symptom exacerbation.[48,49] In a survey of 1,200 patients with IBS, lifestyle changes that patients felt improved their symptoms included eating small meals (69%); avoiding fatty foods (64%); increasing fiber intake (58%); and avoiding milk products (54%), carbohydrates (43%), caffeine (41%), alcohol (27%) and high-protein foods such as meats (21%).[77] Evidence to distinguish whether food allergy or food intolerance occurs in IBS is limited, and patients cannot easily separate the concepts when responding to surveys.[78] Traditionally, a food

allergy is thought to be caused by enhanced activation of the immune system with release of histamine from mast cells, while a food intolerance is considered to be a physiologic disturbance not associated with an immune response. More recently, some of the proposed mechanisms by which food allergy or intolerance may result in increased IBS symptoms include triggers by food antigens, changes in gut microbiota, low-grade mucosal immune activation, or endogenous chemical irritation (bile salts), which may manifest as secretory, absorptive, sensory and motility disturbances in the gastrointestinal tract.[48] In a systematic review of food allergy and intolerance in IBS, response rates to exclusion diets varied from 15% to 71%.[48] Owing to insufficient evidence, the ACG IBS Task Force does not recommend the use of exclusion diets outside of clinical trials for the management of IBS.[45]

Although mucosal immune activation by food antigens has been suggested to cause food allergies in IBS, the only supportive evidence includes a positive response to exclusion diets and to disodium cromoglycate.[79] There are also data demonstrating that patients with IBS have increased atopy,[80] asthma,[81] and airway responsiveness to methacholine challenge.[82] No gold standard diagnostic test for food allergy exists.[83] A positive result of a skin prick test and radioallergosorbent test (RAST) suggests that systemic inflammation (IgE mediated) is present, but these tests can even be positive without symptoms. The basophil activation test, which uses flow cytometry, has been found to have a superior sensitivity and comparable specificity to total serum IgE and food-specific IgE in diagnosing food hypersensitivity in patients with IBS symptoms.[84]

Clinical response to uncontrolled dietary gluten exclusion was investigated in a group of 41 IBS-D patients without biopsy-proven celiac disease.[66] Response to a gluten-free diet was defined as resolution of diarrhea (<3 formed stools daily) and decrease in gastrointestinal symptom score (abdominal pain, distention, borborygmus, bloating and fullness). Statistically significant decreases in serum IgG antibodies to gliadin and tissue transglutaminase were seen in the IBS-D group after gluten exclusion. After 6 months, stool frequency and symptom score returned to normal values in 60% of patients with IBS-D who had positive celiac serologies and HLA-DQ2 status and in 12% who were negative for both. These findings need to be confirmed in larger, controlled trials but suggest that celiac disease markers may be able to identify patients with IBS-D who will respond to a gluten-free diet.

Patients with IBS have a higher prevalence of lactose maldigestion and symptoms of subjective lactose intolerance (even without evidence of lactose maldigestion) compared with healthy controls.[45] As lactose intolerance can mimic the symptoms of IBS, it is recommended that patients keep a food diary to assess if their gastrointestinal symptoms are associated with dairy products.[45] Dairy products should be avoided or minimized if their intake is consistently associated with the onset or exacerbation of IBS symptoms.

Table 2 | Histological findings in patients with IBS and controls[67]

Lesion	Patients with IBS (*n* = 466) (%)	Controls (*n* = 451) (%)	*P* value
Adenomas	36 (7.7)	118 (26.1)	<0.0001
Hyperplastic polyps	39 (8.4)	52 (11.5)	NS
Colorectal adenocarcinoma	0 (0.0)	1 (0.2)	NS
IBD	2 (0.4)	0	NS
Microscopic colitis	7 (1.5)	NA*	NA
Solitary rectal ulcer syndrome	1 (0.2)	1 (0.2)	NS

*Number of controls with microscopic colitis is not recorded, as those participants did not undergo systematic random colon mucosa biopsies. Abbreviations: NA, not available; NS, not significant.

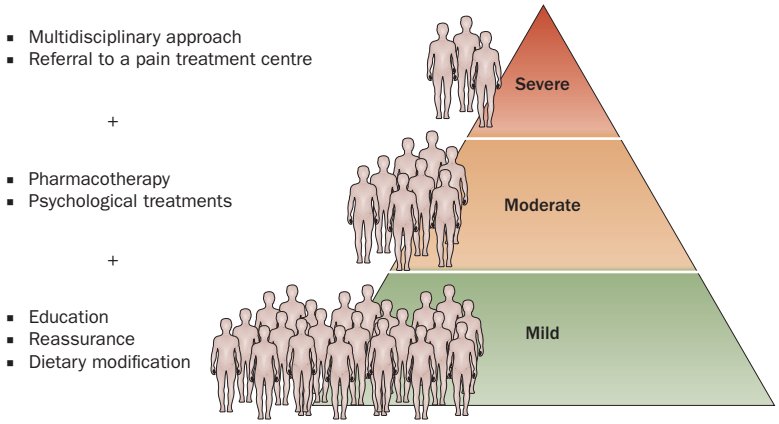

Figure 1 | Graduated treatment approach for IBS. A graduated treatment approach has been suggested for the management of patients with IBS. For mild symptoms, education, reassurance and dietary adjustment can suffice. For moderate symptoms, identification and modification of exacerbating factors, psychotherapeutic and/or behavioral techniques and pharmacological therapy aimed at the predominant symptoms are recommended. For severe symptoms, physician-based behavior modification and psychopharmacologic agents are useful. For intractable symptoms, referral to a pain treatment center may be needed. Permission obtained from D. Drossman, Rome Foundation.

Evidence is also increasing of an association between IBS symptoms and fructose intolerance.[85] Fructose is mainly found in three dietary forms: free fructose (for example, in fruits); as a component of the disaccharide sucrose; or as fructans, a polymer of fructose (for example, in vegetables).[86] When fructose is not completely absorbed in the small intestine and reaches the colon, it is fermented by bacteria to hydrogen, carbon dioxide and small chain fatty acids.[86] The osmotic load and gas production can have a laxative effect and result in IBS symptoms of bloating and abdominal discomfort.[85] A related group of short chain carbohydrates and sugar alcohols (fermentable oligo-, di- and monosaccharides and polyols, also known as FODMAPs) has been suggested to induce abdominal symptoms of bloating, nausea, vomiting, pain and altered bowel habits, especially in patients with IBS.[87] FODMAPs include foods that contain fructose in excess of glucose (for example, apples and pears), fructan-containing vegetables (for example, onions, asparagus and artichokes), wheat-based products (for example, bread and pasta), sorbitol-containing foods (for example, plums, cherries and artificial sweeteners) and raffinose-containing foods

(for example, cabbage and lentils). In a controlled study of 26 patients with IBS, the FODMAP exclusion diet was shown to be efficacious, leading to global symptom improvement in over 80% of patients with IBS who had fructose intolerance.[85]

In summary, most but not all patients with IBS report meal-related symptoms, which may be due, in part, to food intolerances or hypersensitivities and increased visceral perception. While lactose and fructose intolerance can increase IBS symptoms, they are usually coexistent with IBS rather than the primary cause of IBS symptoms. A food and symptom diary may help patients determine certain foods that trigger symptoms, although patients often report an inconsistent association of these foods with IBS symptoms. When they are experiencing a flare in their IBS symptoms, some foods are quite bothersome but can be well tolerated when their IBS is in remission.

Treatment options for IBS-C

Fiber and bulking agents

Conventional bulking agents include psyllium, methylcellulose and calcium polycarbophil. Fiber supplementation is usually used as first-line treatment of constipation in IBS; however, doses should be gradually titrated to limit the adverse effects of bloating and flatulence. Ford and colleagues conducted a systematic review of 12 trials evaluating the efficacy of various forms of fiber for overall symptom relief in IBS ($n = 591$).[88] 52% of patients taking fiber had persistent symptoms compared with 57% who received placebo (relative risk [RR] 0.87, 95% CI 0.76–1.00). However, only two of the included trials recruited patients with IBS-C specifically.[88] Wheat bran failed to significantly improve IBS symptoms, with persistent symptoms in 54% of patients in both the bran and placebo groups.[88] In four of the six studies that randomly allocated patients to receive ispaghula husk (a derivative of psyllium) or placebo, 52% of patients who received active treatment had persistent symptoms compared with 64% of patients who received placebo (RR 0.78, 95% CI 0.63–0.96), which suggests significant efficacy of this fiber supplement for improving symptoms. However, there was considerable heterogeneity in the quality of the studies. When only high-quality studies were considered, the difference in symptoms was only marginally significant.[88]

In a study by Bijkerk *et al.*,[89] 275 patients with IBS (56% IBS-C, 25% IBS-D, 19% IBS-A) were randomly allocated to 12 weeks of daily treatment with 10 g psyllium, 10 g bran or 10 g placebo. More patients allocated to psyllium, but not bran, responded to treatment (defined as more than 2 weeks of adequate relief of abdominal pain and discomfort in the past month) in the first 2 months than patients allocated to receive placebo, but by the third month a similar number of patients from the psyllium and placebo groups were responding to treatment. The change in severity of symptoms was highest in the psyllium group compared with bran and placebo. However, no significant differences occurred between the three groups with respect to improvements in abdominal pain or quality of life scores.

Laxatives

Osmotic laxatives (for example, polyethylene glycol [PEG] and lactulose) and stimulant laxatives (for example, bisacodyl and senna) are commonly used to treat chronic constipation, but their efficacy in IBS-C has not been well studied. The efficacy of PEG alone or in combination with tegaserod for the treatment of IBS-C was shown in a small study of adolescents with IBS-C.[90] PEG alone was associated with a significant increase in stool frequency from a mean of 2.07 ± 0.62 to 5.04 ± 1.51 bowel movements per week, but pain intensity remained unchanged. PEG combined with tegaserod led to a significant increase in stool frequency and a significant decrease in pain. Osmotic laxatives may be limited by adverse effects of bloating and flatulence. The use of stimulant laxatives can be associated with abdominal cramping, electrolyte depletion and diarrhea.[91]

Chloride channel activators

Lubiprostone—a prostaglandin derivative and a selective chloride channel activator—facilitates transport of chloride, sodium and water into the intestinal lumen. Lubiprostone is FDA approved for the treatment of chronic idiopathic constipation in men and women at a dose of 24 μg twice daily and in women with IBS-C at a dose of 8 μg twice daily. In a phase II, dose-ranging study in IBS-C, daily doses of lubiprostone ranging from 16 μg to 48 μg significantly improved IBS symptoms; however, adverse effects were increased at the higher doses.[92] In phase III trials, lubiprostone at a dose of 8 μg twice daily for up to 12 weeks showed significant benefit over placebo (overall responders:17.9% versus 10.1%) in patients with IBS-C (mainly women).[93] The primary end point was quite restrictive, which explains the low responder rates in both the lubiprostone and placebo groups. Significant improvements in the secondary outcomes of abdominal discomfort and/or pain, bloating, stool consistency and constipation severity were demonstrated. There was a trend for overall improvement of IBS-QOL and significant improvement in the health worry and body image domains. Reported adverse effects of lubiprostone include nausea, diarrhea and abdominal pain. Lubiprostone is contraindicated in gastrointestinal obstruction and pregnancy (Category C rating after studies in animals showed increased fetal resorption).[45]

Tegaserod

Tegaserod is a 5-HT_4 receptor agonist that has been shown to be efficacious in men and women with chronic constipation[94] and in women with IBS-C.[95] A systematic review of the efficacy of tegaserod versus placebo, which included 11 well-designed clinical trials ($n = 9,242$), showed that symptoms persisted in 55% of patients who received tegaserod compared with 63.5% who received placebo (RR 0.85, 95% CI 0.80–0.90).[96] However, tegaserod was withdrawn from the market in 2007 as data from trials (88% female patients with IBS) showed that tegaserod ($n = 11,614$) had a 0.11% increased risk of cardiovascular events (myocardial infarction, stroke, transient ischemic attack) compared with 0.01% risk with

Table 3 | Treatment options for IBS-C

Drug class	Generic name (dose)	Key points
Bulking agents	Psyllium (2.5–30 g daily in divided doses) Methylcellulose (500 mg, 1–2 tablespoons daily or up to three times daily) Calcium polycarbophil (1,250 mg twice or four times daily)	May improve straining and hard stools Benefit mainly shown with psyllium
Osmotic laxatives	Milk of magnesia (400 mg/5 ml, 10–20 ml up to four times daily) Lactulose (10–20 g/15–30 ml daily) Polyethylene glycol (17 g in 237 ml solution daily)	Used clinically for treatment of constipation but efficacy in IBS has not been well studied
Stimulant laxatives	Senna (15 mg daily) Diphenylmethane derivatives (for example, bisacodyl at a dose of 10 mg, 1–2 tablets daily or 1 suppository daily)	Used clinically for treatment of constipation but efficacy in IBS has not been well studied
Emollient laxatives	Docusates (100 mg, 1–3 tablets daily) Mineral oil (5–10 cm^3 daily)	Used clinically for treatment of constipation but efficacy in IBS has not been studied
5-HT_4 agonist	Tegaserod (6 mg twice daily)	Only available for emergency use by FDA due to reported cardiovascular risks
Chloride channel activator	Lubiprostone (8 μg twice daily with meals)	Approved by FDA for IBS-C in women, and chronic idiopathic constipation in men and women Consider increasing dose to 24 μg twice daily if no response with lower dose

Abbreviation: IBS-C, constipation-predominant IBS.

placebo ($n = 7{,}031$).[97] In the USA, tegaserod is available only under an FDA emergency drug protocol (Table 3).

Treatment options for IBS-D

Loperamide

Antidiarrheal agents, such as loperamide, are used routinely in many patients with IBS-D to provide symptomatic relief by reducing stool frequency and incontinence, and improving stool consistency. Loperamide acts on mu-opioid receptors in the myenteric plexus, resulting in slowed colonic transit, and thus increased solidification of stool. The ACG IBS Task Force systematic review assessed efficacy data from two randomized, controlled trials[98,99] of loperamide and found that it was not more effective than placebo at reducing abdominal pain or global symptoms of IBS (RR of symptoms not improving 0.44, 95% CI 0.14–1.42) but was effective in improving stool consistency and frequency in patients with diarrhea.[45] An additional study that was not included in this review was a 5-week controlled trial that included 99 patients with IBS of varying subtypes. This study found that loperamide improved stool consistency, stool frequency and/or pain intensity in about one-third of patients.[100] The BSG guidelines acknowledge the efficacy of loperamide in reducing diarrhea but not abdominal pain, and also suggest the use of loperamide on a scheduled or as needed basis for symptom relief without risk of tachyphylaxis after chronic use.[17]

Alosetron

Alosetron is a centrally and peripherally acting 5-HT_3 antagonist that inhibits gastrointestinal motility and reduces visceral sensitivity and abdominal pain.[101] The quality of evidence for 5-HT_3 antagonists, including alosetron, is high, but serious adverse events, including complications of constipation and colon ischemia, can occur in a small number of patients[102,103] and therefore limit its use. A systematic review of eight placebo-controlled trials ($n = 4{,}987$) evaluated the effect of alosetron on the adequate relief of abdominal pain and discomfort in patients with IBS-D. The study found that symptoms persisted in 49% of patients who received alosetron compared with 64% of patients who received placebo (RR 0.79, 95% CI 0.69–0.90).[94] Alosetron also demonstrated sustained relief of abdominal pain, discomfort and urgency in patients with IBS-D for up to 48 weeks with its safety being equivalent to that of placebo.[104] In the one male-only study of IBS-D, 1 mg of alosetron given twice daily resulted in significant relief of abdominal pain and discomfort compared with placebo (53% versus 40%, $P = 0.04$), although the results do not seem as robust as that seen in studies of women with IBS-D.[103] Alosetron is only available under a risk management program because of the risk of ischemic colitis and complications of constipation, which typically occur early in the treatment course. An assessment of this risk management program for the past 7 years found persistently low incidence rates of ischemic colitis (0.95 per 1,000 patient-years) and serious complications of constipation (0.36 per 1,000 patient-years), which resolved promptly after termination of therapy.[105] These incidence rates are similar to the rates observed during the postmarketing cycle before alosetron withdrawal.[102] Alosetron is currently prescribed to women with severe symptoms of IBS-D who have failed conventional therapy.

Rifaximin

Rifaximin is an antibiotic that has very low systemic absorption and broad-spectrum activity against Gram-positive and Gram-negative aerobes and anaerobes. It is FDA approved for the treatment of traveler's diarrhea and hepatic encephalopathy. In a phase IIb, multicenter, placebo-controlled study, treatment of IBS-D patients with rifaximin was associated with significantly greater adequate relief of global IBS symptoms (52% versus 44%) and bloating (46% versus 40%), which was maintained

at the end of the 12-week follow-up period.[106] Greater efficacy was noted in patients with mild-to-moderate disease, and in those with diarrhea. Before completion of the two phase III, multicenter, randomized, placebo-controlled trials with rifaximin, the ACG IBS Task Force reviewed the existing studies and found that a short-term course of rifaximin was more effective than placebo for global improvement of IBS symptoms and for bloating.[45] In two North American phase III trials (TARGET 1 and TARGET 2), patients with mild-to-moderate, non-constipating IBS were randomly allocated to rifaximin at a dose of 550 mg three times daily or placebo for 2 weeks and followed for up to 3 months. The pooled data showed that a greater proportion of the rifaximin group achieved adequate relief of IBS symptoms compared with the placebo group (40.7% versus 31.7%). The rifaximin group had improved daily assessments of IBS symptoms, bloating, abdominal pain and discomfort over a period of 3–6 weeks, and greater likelihood of sustained relief of symptoms over 3 months.[107] However, no data are available on the long-term safety and efficacy of nonabsorbable antibiotics for IBS symptoms.[45] The potential consequences of repeated and widespread use of antibiotics in IBS have not been studied. Health-care providers must decide on how and when to use rifaximin on the basis of available data, their clinical experience and the patient's interest and concerns about taking this medication. Although there are differing opinions on how rifaximin should be used, we recommend considering its use in patients with mild-to-moderate, nonconstipating IBS and/or in patients with predominant bloating. The recommended dose is 550 mg three times daily for 14 days. Although there are fewer data to support its use in IBS-C, it may still be efficacious in these patients—particularly in those with predominant bloating. A discussion with the patient about the lack of data on long-term efficacy and safety in IBS, prevention of recurrent symptoms, maintenance use, and retreatment for recurrent symptoms is strongly recommended. IBS is a chronic or recurrent condition and patients should be aware of these considerations before agreeing to take this medication.

The association of breath testing for SIBO and treatment response with rifaximin has not been consistently shown. Sharara *et al.*[108] compared the efficacy of rifaximin (at a dose of 400 mg twice daily) and placebo in 124 patients who reported predominant abdominal bloating (56.5% with IBS) but had negative breath tests for SIBO. Rifaximin was associated with a significant improvement in global symptom relief compared with placebo at the end of a 10-day treatment period (41.3% versus 22.9%, $P = 0.03$) and 10-day post-treatment period (28.6% versus 11.5%, $P = 0.02$), which is similar to other rifaximin studies.[107] In addition, there was a significant decrease in bloating-specific scores. In an uncontrolled Italian study of 54 patients with IBS (all subtypes) with positive lactose hydrogen breath tests, patients received rifaximin at a dose of 1,200 mg daily for 7 days. After 3 weeks, the breath tests were repeated and found to be negative in 50% of patients and positive in the other 50% of patients. There was a reduction in symptoms amongst the patients who had negative breath tests, but no reduction in symptoms in the patients who had positive breath tests. This suggests that breath test results may correlate with treatment response; however, larger controlled trials need to be performed.[109] As rifaximin has been efficacious in the treatment of acute diverticulitis of the colon,[110] it is possible that improvement in IBS symptoms associated with rifaximin is not due to an effect on SIBO, but rather on colonic bacteria (Table 4).

Treatment for abdominal pain

Antispasmodics

The pain experienced in IBS is thought to be mediated by central as well as peripheral mechanisms. Pain may be related in part to smooth muscle spasm; hence, smooth muscle and cholinergic receptors are potential drug targets for abdominal pain associated with IBS. In a meta-analysis of 12 trials ($n = 1,778$), 39% of patients who received antispasmodics had persistent symptoms compared with 56% of patients who received placebo (RR 0.68, 95% CI 0.57–0.81).[88] Individual antispasmodics (otilonium, trimebutine, cimetropium, hyoscine and pinaverium) showed significant benefit compared with placebo. However, there was considerable heterogeneity among the studies, as well as a publication bias, which prevents adequate conclusions being drawn from the results.[88] The BSG guidelines state that the use of mebeverine is generally well tolerated on an as needed basis before meals, especially when reassurance fails to improve symptoms.[17] However, a systematic review of the efficacy of mebevirine amongst all IBS subtypes showed no significant improvement in abdominal pain or global symptoms compared with placebo.[111] The ACG IBS Task Force recommend the use of certain antispasmodics (hyoscine, cimetropium and pinaverium) for short-term relief of abdominal pain/discomfort in IBS but acknowledge that long-term efficacy data and data on safety are not available.[45] Commonly reported adverse effects with antispasmodics include dry mouth, dizziness and blurred vision.[88] In clinical practice, antispasmodics can be particularly helpful for postprandial symptoms if taken at least 30 min before meals.

Antidepressants

Antidepressants are used for their effects on the central modulation of visceral afferent input, slowing of gastrointestinal transit, decreased primary afferent nerve fiber firing, and treatment of comorbid psychological conditions. Tricyclic antidepressants (TCAs) inhibit reuptake of norepinephrine and serotonin, and have additional antihistaminergic and anticholinergic activity.[112] In animal studies, TCAs reduced the frequency of nerve impulses induced by noxious colonic distension.[113] TCAs also have an effect on central pain modulation, as demonstrated by amitriptyline reducing brain activation during pain in the anterior cingulated cortex and parietal association cortex during stress in women with IBS.[114]

In a two-site clinical trial, the efficacy of desipramine and placebo in women with moderate to severe

Table 4 | Treatment options for IBS-D

Drug class	Generic name (dose)	Key points
Antidiarrheals	Loperamide (1–8 mg four times daily in divided doses) Diphenoxylate (5 mg up to four times daily)	Useful for the treatment of diarrhea but no global symptom relief shown Titrate dose to desired effect and avoid constipation
5-HT_3 antagonist	Alosetron (0.5–1.0 mg twice daily)	Efficacious for IBS-D Only available for treatment of severe IBS-D in women under a risk management program Concerns of serious complications of constipation and ischemic colitis
Tricyclic antidepressants	Amitriptyline (10–150 mg at night) Doxepin (10–150 mg at night) Imipramine (10–150 mg at night) Clomipramine (25–100 mg at night) Trimipramine (10–150 mg at night) Desipramine (10–150 mg at night) Nortriptyline (10–150 mg at night)	Post hoc analysis of an IBS trial suggests greater efficacy in IBS-D Initiated at lower dose than usual dose for mood disorders Recommend titrating dose for desired effect and to minimize adverse effects
Antibiotics	Rifaximin (400–550 mg three times daily)	Global efficacy demonstrated in nonconstipating IBS Improvement in bloating also demonstrated

Abbreviation: IBS-D, diarrhea-predominant IBS.

functional bowel disorders was evaluated.[115] The primary outcome measure was a composite score of treatment satisfaction, global well-being, average daily pain rating, and disease-specific QOL. Desipramine did not show significant benefit over placebo in overall patient satisfaction ($n = 216$) in the intention-to-treat analysis (responder rate: 60% desipramine versus 47% placebo). However, there was a statistically significant benefit in the per-protocol analysis (responder rate: 73% versus 49%). Subgroup analysis revealed benefit of desipramine over placebo in patients with moderate symptoms, a history of abuse, no depression, and diarrhea-predominant symptoms. Adverse effects included sedation, constipation, tachycardia, palpitations and insomnia but these can be reduced by slow escalation of drug dosage.[112] A meta-analysis of nine studies comparing the efficacy of TCAs with placebo ($n = 575$) found that 132 of 319 patients receiving TCAs (41.4%) had persistent symptoms after treatment compared with 153 of 256 (59.8%) receiving placebo (RR 0.68, 95% CI 0.56–0.83). It should be noted that these studies used different TCAs and doses. In clinical practice, the use of low starting doses (for example, 10–25 mg every night) with a gradual increase to a dose associated with a desired effect, while minimizing adverse effects, is recommended.

Selective serotonin reuptake inhibitors (SSRIs) inhibit the re-uptake of serotonin (5-HT) by blocking the 5-HT transporter protein at presynaptic nerve endings and increasing synaptic exposure to a higher concentration of 5-HT.[112] There is not enough evidence to support the use of SSRIs for relief of abdominal pain in IBS; however, they are used to improve overall well-being, reduce anxiety associated with IBS and augment the effects of TCAs.[112] In a meta-analysis of five studies that used SSRIs versus placebo ($n = 230$), 44.2% of patients allocated to SSRIs had persistent symptoms following therapy compared with 70.9% of patients who received placebo (RR 0.62, 95% CI 0.45–0.87).[115] Nonetheless, these studies enrolled relatively small numbers of patients. A notable side effect of SSRIs is diarrhea, and thus they may be beneficial for patients with IBS-C.[112] High-quality, larger studies are needed to determine if SSRIs can relieve IBS symptoms, including abdominal pain, irrespective of their effects on mood (Table 5).

Psychological and behavioral therapy

Cognitive behavioral therapy (CBT), dynamic psychotherapy, hypnotherapy and stress management reduce the symptoms of IBS.[45] These therapies can address the interference of IBS on daily functioning and HRQOL, the psychological impact of stressors or traumatic events associated with symptom onset or exacerbations, and coexistent psychological symptoms. In a study by Drossman *et al.*[116] of 431 patients with functional bowel disorders who underwent CBT or education treatment for 12 weeks, CBT was significantly more effective in improving the overall composite score, global well-being and satisfaction with treatment than education (responder rate: 70% CBT versus 37% education, $P < 0.0001$). CBT was beneficial over education for all subgroups, except for patients with depression. In this study, CBT focused on developing more effective coping mechanisms via modifying maladaptive cognitions regarding gastrointestinal illness to more positive ones. In another study, by Lackner *et al.*,[117] 75 patients with IBS (86% female) were assigned to therapist-administered CBT, patient-administered CBT or control (waiting list, no CBT) for 10 weeks. At the end of treatment, both CBT groups were superior to the control group with respect to the percentage of patients reporting adequate relief from pain and/or discomfort (patient-administered CBT, 72%; therapist-administered CBT, 60.9%; control, 7.4%) and improvement of symptoms. CBT-treated patients experienced significant improvements in IBS-QOL and IBS symptom severity but not psychological distress compared with the control group. Lackner *et al.*[118] studied 71 patients with moderately severe IBS and found that 95.2% of rapid responders (positive response to CBT by week 4) showed treatment response at a 3-month follow-up compared with 28% of nonrapid responders

Table 5 | Treatment options for pain and/or bloating

Drug class	Generic name (dose)	Key points
Antispasmodics	Hyoscamine sulfate (0.125 mg sublingually or by mouth up to four times daily) Dicyclomine (10–20 mg by mouth twice daily or up to four times daily) Clidinium + chlordiazepoxide (2.5 mg/5 mg, 1–2 tablets up to three or four times daily) Hyoscamine + scopolamine + atropine + phenobarbital (1–2 tablets up to three or four times daily)	Limited proven efficacy in IBS but may be helpful for postprandial symptoms Can be used as needed To be taken before meals
Tricyclic antidepressants	Amitriptyline (10–150 mg at night) Doxepin (10–150 mg at night) Imipramine (10–150 mg at night) Clomipramine (25–100 mg at night) Trimipramine (10–150 mg at night) Desipramine (10–150 mg at night) Nortriptyline (10–150 mg at night)	Post hoc analysis of an IBS trial suggests greater efficacy in IBS-D Initiated at lower dose than usual dose for mood disorders Recommend titrating dose for desired effect and to minimize adverse effects
Selective serotonin reuptake inhibitors	Fluoxetine (10–40 mg daily) Citalopram (20 mg daily) Paroxetine (20–50 mg daily) Sertraline (25–100 mg daily) Escitalopram (10 mg daily)	Limited studies suggest improvement in overall well-being Large, randomized, controlled trials in IBS are needed
5-HT_4 agonist	Tegaserod (6 mg twice daily)	Only available for emergency use by FDA due to cardiovascular risks
Antibiotics	Rifaximin (400–550 mg three times daily)	Studies demonstrate relief of bloating
Probiotics	*Bifidobacterium infantis* (1 tablet daily) VSL #3 (1 packet twice daily)	High-quality studies are lacking *Bifidobacterium infantis* improves IBS symptoms Probiotic studies in general have suggested improvement in gas-related symptoms

(P<0.001). Rapid responders were more likely than non-rapid responders to attribute their symptoms to their own behavior, to express more confidence in their ability to control symptoms by changing specific behaviors and had more motivation to participate in a self-management program. In another study, maladaptive behaviors (for example, avoidance behaviors, such as avoiding situations associated with worsening symptoms) at baseline correlated with less disability at 12 months in patients who received CBT combined with an antispasmodic but not in those who received only an antispasmodic.[119]

Although studies that provide guidance for the ideal timing of psychological or behavioral treatment are lacking, these interventions are often used in patients with treatment refractory disease, and may also be a useful adjunctive therapy.[17] Patients who are likely to benefit most from these therapies are those who are willing to accept a significant psychological component to their symptoms, and those who would prefer a talking therapy over drug therapy.[17] In general, CBT has been found to be less effective in patients with high baseline levels of anxiety or depression.[120–122]

Gut directed hypnotherapy (that is, use of therapeutic qualities of conventional hypnotherapy focused towards control of gut function to help reduce symptoms) has been studied for the treatment of IBS, and aims to reassure the patient and provide focus on their symptom improvement. In a Cochrane review published in 2007, four studies were assessed and found to demonstrate the superior efficacy of hypnotherapy for improving abdominal pain and composite primary IBS symptoms compared with waiting list controls or usual medical management.[123] Whorwell *et al.*[124] demonstrated a marked improvement in abdominal pain, abdominal distension, general well-being and bowel habit in 30 patients with severe refractory IBS who received hypnotherapy compared with psychotherapy. Baseline psychological symptoms were not predictive of IBS symptom response to hypnotherapy.[125]

In summary, psychological or behavioral treatments can be effective in the management of IBS and can be used alone or in combination with pharmacologic therapies. However, these studies should be interpreted with caution as most are relatively small and considered to be of suboptimal quality.[45] The main considerations for implementing behavioral or psychological therapy are a patient's motivation and interest in the treatment, finding an experienced therapist near the patient and the cost of the treatment (Table 6).

Complementary alternative therapies

Probiotics

Probiotics, such as *Lactobacillus* and *Bifidobacteria*, are nonharmful pathogens that can positively influence digestive health. Postulated modes of action include binding to epithelial cells and inhibition of pathogen binding, enhanced barrier function, acidification of the colon by changes in nutrient fermentation, alteration in mucosal response to stress, immunomodulatory actions and inhibition of visceral hypersensitivity.[126] Probiotics can vary in species, strains, preparations and doses, which makes the interpretation of efficacy data in the literature difficult.

Studies evaluating the efficacy of *Bifidobacterium infantis* 35624 are considered the only high-quality

Table 6 | IBS treatment options for global symptoms and/or overall well-being

Treatment	Key points
Psychological and behavioral therapy	
Cognitive behavioral therapy	Modifies maladaptive behaviors and thoughts Improves global IBS symptoms
Hypnotherapy	Improves IBS symptoms
Complementary alternative medicine	
Acupuncture	Improvement in IBS symptoms has not been shown in controlled trials Placebo effects produce clinically significant improvement The patient–practitioner relationship is the most robust component of the placebo effect
Chinese herbal therapy	May help with improving symptoms, but no high-quality studies performed Concerns raised about possible adverse effects

Table 7 | Emerging therapies in IBS[135,136]

Drug class	Name	Mechanism of action
IBS-C		
Ileal bile acid transporter inhibitor	IBAT inhibitor A3309[137]	Partially blocks the reabsorption of bile acids in the ileum leading to an increase in bile acids in the colon, which results in increased secretion and colonic motility
Guanylate cyclase C agonist	Linaclotide	Increases chloride and bicarbonate secretion into intestinal lumen
Opioid antagonist	Naloxone, naltrexone	Decreases intestinal fluid absorption and decreases inhibition of peristalsis and secretion
5-HT_4 agonist	Prucalopride	Increases intestinal motility
Bile acid	Sodium chenodeoxycholate[138]	Induces electrolyte secretion and accelerates colonic transit
IBS-D or nonconstipating IBS		
κ-Opioid receptor agonist	Asimadoline	Activates opioid receptors, which may reduce visceral perception
Carbon-based adsorbent	AST-120[139]	Adsorbs luminal substances including serotonin and bile acids
CRF antagonists	Pexacerfont, GW876008	Blocks CRF_1 receptors to potentially decrease gastrointestinal motility and visceral sensitivity
Proanthocyadin	Crofelemer	Reduces chloride ion secretion via CFTR channel
2,3-Benzodiazepine modulator	Dextofisopam	Modulates autonomic responses
SNRI	DDP-225	May increase synaptic levels of norepinephrine to reduce visceral pain; inhibits intrinsic cholinergic neurons
Serotonin synthesis inhibitor	LX1031[140]	Reduces gastrointestinal levels of serotonin
5-HT_3 antagonist	Ramosetron	Blocks 5-HT_3 receptors to slows gastrointestinal transit and decreases visceral sensitivity
Pain and/or discomfort		
SSRIs and SNRIs	Antidepressants	Blocks reuptake of serotonin (SSRI, SNRI) and norepinephrine (SNRI)
Glucagon-like peptide-1 analogue	ROSE-010[141]	Inhibits small intestinal motility

Abbreviations: 5-HT, serotonin; CFTR, cystic fibrosis transmembrane conductance regulator channel; CRF, corticotropin-releasing factor; IBS-C, constipation-predominant IBS; IBS-D, diarrhea-predominant IBS; SSRI, selective serotonin reuptake inhibitor; SNRI, serotonin and norepinephrine reuptake inhibitor.

probiotic trials that have showed repeated efficacy.[127] In a randomized, placebo-controlled trial of *Lactobacillus salivarius* UCC4331 and *B. infantis* 35624 each in a milk extract for 8 weeks, a significantly greater reduction in composite symptom scores (abdominal pain and/or discomfort, bloating and/or distension, and bowel habit difficulty) compared with placebo was demonstrated for the *Bifidobacterium* group but not the *Lactobacillus* group.[128] In a subsequent 4-week, placebo-controlled trial of 362 patients with IBS, encapsulated *B. infantis* 35624, at a dose of 1×10^8 cfu, was found to be superior to placebo in reducing abdominal pain, bloating, bowel dysfunction, incomplete evacuation, straining and the passage of gas, but only during the fourth week of treatment. Global symptom improvement in the *Bifidobacterium* group exceeded that of placebo by 20%.[129] Interestingly, the efficacies of both 1×10^6 and 1×10^{10} cfu doses were not different from that of placebo. It should be noted that there were problems with the bioavailability of the 1×10^{10} dose, which may have confounded study results. No significant adverse events were recorded with any of the doses tested. However, the safety and tolerability of probiotics has not been rigorously assessed.

Acupuncture

A Cochrane review published in 2006 examined six randomized, placebo-controlled trials of acupuncture versus sham acupuncture in IBS, but owing to the poor quality of the studies the results were inconclusive.[130] In a subsequent study of 43 patients with IBS who were randomly allocated to acupuncture or sham acupuncture, there was no significant difference in the response rates on quality of life measures between the two groups.[131] Lembo *et al.*[132] conducted a study in 230 patients with IBS who were assigned to 3 weeks of true or sham acupuncture (six treatments) after a 3-week run-in period of sham acupuncture. No significant differences between the groups were found with respect to the IBS Global Improvement Scale, IBS Symptom Severity Scale, IBS Adequate Relief or IBS-QOL.[132] In 2008, the same group of investigators studied 262 patients with IBS who were assigned to one of three groups: waiting list (observation), placebo acupuncture alone ('limited'), or placebo acupuncture with a patient–practitioner relationship augmented by the practitioner's warmth, attention and communication of confidence and positive expectation ('augmented').[133] All treatment outcome measures were more pronounced in the group who received placebo acupuncture with an augmented patient–practitioner relationship. The authors concluded that placebo effects produce clinically significant improvements, and that the patient–physician relationship is the most robust component of the placebo effect.

Chinese herbal therapy

A systematic review evaluating the efficacy of herbal therapy in 75 randomized, placebo-controlled studies with a total of 7,957 patients with IBS was published in 2006. The study concluded that some herbal therapies may have benefit in IBS, but poor quality of study design, questionable purity of these compounds and concern over serious adverse effects limit their use.[134] High-quality studies are needed to confirm the efficacy of herbal therapies (Table 6).

Conclusions

IBS is a prevalent chronic or recurrent gastrointestinal condition that substantially affects patients' quality of life and is associated with a considerable health-care and economic burden. Although a reliable biomarker for the diagnosis of IBS is yet to be found, the development of symptom-based diagnostic criteria have enabled research studies to evaluate the symptoms, pathophysiologic mechanisms and treatment responses of a more homogenous group of patients than prior to the development of standardized criteria, and to move away from considering IBS as a diagnosis of exclusion.

Multiple treatment options are available for IBS, although most do not effectively improve symptoms in all patients even within a particular subtype. Predominant symptoms, severity of the IBS and patient and practitioner preferences usually guide management. Given the complex and multifactorial nature of IBS, the optimal treatment is often individualized and patient-centered. As the pathophysiology of IBS is defined more clearly with future research, more effective diagnostic and therapeutic strategies will become available. A number of emerging therapies with novel mechanisms of action are currently being investigated in IBS (Table 7).

Review criteria

A MEDLINE search was conducted for English-language publications up to and including June 2010 pertaining to the diagnosis and management of IBS. The following search terms were used: "irritable bowel syndrome"; "IBS"; "IBS diagnosis"; "IBS management"; "IBS-constipation"; "IBS-diarrhea"; "IBS pain"; "IBS bloating"; "IBS" and the following search terms: "diagnostic testing", "colonoscopy", "SIBO", "diet", "food allergy", "gluten", "food intolerance", "bulking agents", "laxatives", "chloride channel activators", "$5HT_3$ antagonists", "$5HT_4$ agonists", "antidiarrheal", "rifaximin", "antispasmodics", "antidepressants", "psychological therapy", "behavioural therapy", "hypnotherapy", "probiotics", "acupuncture", "herbal therapy", "health care utilization". Search limits included humans, men and women, adults (that is, >18 years) and randomized, controlled trials. The papers searched were full text when available. References from relevant papers were manually searched to identify further relevant manuscripts.

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