

WJG 20th Anniversary Special Issues (4): Irritable bowel syndrome**Irritable bowel syndrome: Pathogenesis, diagnosis, treatment, and evidence-based medicine**

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Abstract

Irritable bowel syndrome (IBS) is a chronic and debilitating functional gastrointestinal disorder that affects 9%-23% of the population across the world. The percentage of patients seeking health care related to IBS approaches 12% in primary care practices and is by far the largest subgroup seen in gastroenterology clinics. It has been well documented that these patients exhibit a poorer quality of life and utilize the health care system to a greater degree than patients without this diagnosis. The pathophysiology of IBS is not clear. Many theories have been put forward, but the exact cause of IBS is still uncertain. According to the updated ROME III criteria, IBS is a clinical diagnosis and presents as one of the three predominant subtypes: (1) IBS with constipation (IBS-C); (2) IBS with diarrhea (IBS-D); and (3) mixed IBS (IBS-M); former ROME definitions refer to IBS-M as alternating IBS (IBS-A). Across the IBS subtypes, the presentation of symptoms may vary among patients and change over time. Patients report the most distressing symptoms to be abdominal pain, straining, myalgias, urgency, bloating and feelings of serious illness. The complexity and diversity of IBS presentation makes treatment difficult. Although there are reviews and guidelines for treating IBS, they focus on the efficacy of medications for IBS symptoms using

high-priority endpoints, leaving those of lower priority largely unreported. Therefore, the aim of this review is to provide a comprehensive evidence-based review of the diagnosis, pathogenesis and treatment to guide clinicians diagnosing and treating their patients.

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Key words: Irritable bowel syndrome; Pathogenesis; Diagnosis; Treatment; Evidence-based medicine

Core tip: Irritable bowel syndrome (IBS) has been well documented; these patients exhibit a poorer quality of life and utilize the health care system to a greater degree than patients without this diagnosis. The pathophysiology of IBS is not clear. Many theories have been put forward, but the exact cause of IBS is still uncertain. The complexity and diversity of IBS presentation makes treatment difficult. Although there are reviews and guidelines for treating IBS, they focus on the efficacy of medications for IBS symptoms. Therefore, the aim of this review is to provide a comprehensive evidence-based review of the diagnosis, pathogenesis, prevention and treatment to guide clinicians diagnosing and treating their patients.

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INTRODUCTION

Irritable bowel syndrome (IBS) is a gastrointestinal (GI) disorder characterized by altered bowel habits in association with abdominal discomfort or pain in the absence of detectable structural and biochemical abnormalities^[1].

The understanding of IBS has undergone a rapid evolution with scientific advancement, but historically it was recognized over 150 years ago. In 1849, Cumming reported, “The bowels are at one time constipated, another lax, in the same person. How the disease has two such different symptoms I do not profess to explain”^[2]. IBS is a common functional bowel disorder that generates a significant health care burden and can severely impair quality of life and is the most commonly diagnosed gastrointestinal condition. The etiology is poorly understood and many factors are involved. Understanding the pathogenesis of IBS is important because today’s newer pharmacotherapy agents are beginning to target the known pathophysiological mechanisms of IBS^[3]. Altered gastrointestinal motility, visceral hypersensitivity, post infectious reactivity, brain-gut interactions, alteration in fecal micro flora, bacterial overgrowth, food sensitivity, carbohydrate malabsorption, and intestinal inflammation all have been implicated in the pathogenesis of IBS^[3]. However, the perceived symptoms from these mechanisms consist of abdominal pain or discomfort, bloating, diarrhea, and constipation. Not all symptoms are gastrointestinal, for instance, fatigue is very common. Historically, medical management has focused on symptomatic treatment of these individual complaints^[3]. Serotonin is largely present in the enterochromaffin cells in the gut and is a major regulator of the peristaltic reflex and sensory relays in the gut^[4]. There are two lines of evidence supporting the view that serotonin regulation is abnormal in IBS. The release of serotonin in plasma appears to be reduced in those with constipation-predominant IBS (IBS-C) and increased in diarrhea-predominant IBS (IBS-D)^[5]. A defect in serotonin signaling was noted in both IBS and ulcerative colitis, with a reduction in normal mucosal serotonin and serotonin transporter immunoreactivity in both diseases^[6].

Studies have also begun to focus on the molecular level with serotonin receptor agonists and antagonists. The role of psychosocial factors in IBS also must be considered because these factors influence treatment options and patients’ expectations. According to an American Gastroenterology Association (AGA) technical review^[7], research into this area has yielded four general observations. First, psychological stress exacerbates gastrointestinal symptoms magnifying the severity of diarrhea, abdominal discomfort, and so on.

Next, psychological and psychiatric co morbidity is often represented among IBS patients. These psychosocial factors influence the illness experience, patient expectations, and treatment outcome of IBS patients. Lastly, the AGA emphasizes that these factors also dictate which patients consult physicians. All these considerations must be kept in mind when considering long-term treatment goals *via* pharmacotherapy or psychological management.

Functional GI disorders (FGID), most notoriously functional dyspepsia (FD) and IBS, take a prominent place within the “functional somatic syndromes”, together with chronic fatigue syndrome and fibromyalgia,

with which they frequently overlap^[8]. FGID are frequent disorders of which the pathophysiology is incompletely understood. Psychosocial factors are believed to influence GI sensorimotor function and/or symptom generation in FGID as predisposing, precipitating or perpetuating factors; comorbidity with psychiatric disorders, mostly mood or anxiety disorders is frequent^[8]. Modern epidemiological, psychophysiological and functional brain imaging research has partially clarified the mechanisms through which these psychosocial factors may act on GI function or symptomatology^[8], although the exact nature of their relationship remains a matter of controversy. The “brain-gut axis” can be conceptualized as the bidirectional connection system between the GI tract (with its enteric nervous system) and the brain (central nervous system) through (autonomic) neural, neuroimmune and neuroendocrine pathways. Thus, when gut function is disturbed, the cause of this disturbance can be found in the GI tract itself or in the modulatory input from the central nervous system *via* the brain-gut axis^[8]. The percentage of patients seeking health care related to IBS approaches 12% in primary care practices and is by far the largest subgroup seen in gastroenterology clinics^[7]. It has been well documented that these patients exhibit a poorer quality of life and utilize the health care system to a greater degree than patients without this diagnosis but have other FGID^[9,10]. Patients with IBS visit the doctor more frequently, use more diagnostic tests, consume more medications, miss more workdays, have lower work productivity, are hospitalized more frequently, and consume more overall direct costs than patients without IBS. In this review, an evidence based diagnosis, pathogenesis, and treatment will be presented, to guide clinicians diagnosing and treating their patients.

DEFINITION AND EPIDEMIOLOGY

IBS is a chronic and debilitating functional gastrointestinal disorder that affects 9%-23% of the population across the world (World Gastroenterology Organization, 2009)^[11]. Over the past 20 years, the definition of IBS has evolved, driven largely by expert opinion and based on studies that have identified symptoms that discriminate those labeled as IBS from organic disease, as well as factor analyses that have identified clear symptom clusters. Classically, IBS presents with abdominal pain or discomfort that is relieved by defecation or is associated at its onset with a change in stool frequency (either an increase or decrease) or a change in the appearance of the stool (to either loose or hard). The absence of red flag (alarm) symptoms such as gastrointestinal bleeding, weight loss, fever, anemia or an abdominal mass support such a symptom complex as IBS rather than as structural disease^[12]. A number of other comorbid conditions may occur more often than expected by chance in those with IBS, including gastro-esophageal reflux, genito-urinary symptoms, fibromyalgia, headache, backache and psychological symptoms^[13]. Hence, IBS can present to a number

of different subspecialists and is often initially misdiagnosed^[13].

IBS can be subdivided into those who tend to have predominant diarrhea or predominant constipation^[1,13,14]. There is also a group of IBS patients who have mixed constipation and diarrhea. To complicate matters, those with one predominant bowel pattern can alternate with the other. Highly variable bowel symptoms support a diagnosis of IBS, but the coexistence of abdominal pain and disturbed defecation remains a sine qua non for diagnosis. According to WHO DMS-IV code classification for IBS and its subcategories, IBS can be classified as either diarrhea-predominant (IBS-D), constipation-predominant (IBS-C), or with alternating stool pattern (IBS-A) or pain-predominant. In some individuals, IBS may have an acute onset and develop after an infectious illness characterized by two or more of the following: fever, vomiting, diarrhea, or positive stool culture. This post-infective syndrome has consequently been termed “post-infectious IBS” (IBS-PI)^[15].

IBS is a remarkably common condition according to population-based studies^[13,14,16]. In Western countries, including the United States and Australia, approximately 10% of the general population fulfills the Rome III criteria for IBS, although many do not ever consult for the problem. IBS overlaps with a number of other unexplained gastrointestinal symptom complexes, including chronic constipation and dyspepsia, suggesting that these conditions may not be discrete entities, but represent disorders with a common aetiopathogenesis^[17]. In the West, there tends to be a female predominance but this is not seen in the East. It has been postulated that IBS is under diagnosed in Asia and the condition will increase in prevalence because of changes in diet and infectious risk factors^[18].

PATHOPHYSIOLOGY

Traditionally, IBS has been conceptualized as a condition of visceral hypersensitivity (leading to abdominal discomfort or pain) and gastrointestinal motor disturbances (leading to diarrhea or constipation)^[7,14]. The gastrointestinal motor disturbances identified, including changes in intestinal transit, do not easily explain mixed or alternating IBS^[14]. Some have suggested that these abnormalities are secondary to psychological disturbances rather than being of primary relevance. However, not all patients with IBS have significant psychological overlay and referral bias may partly account for the psychological associations^[7,14]. Hints as to why visceral hypersensitivity and gastrointestinal motor disturbances may arise are emerging. There is increasing evidence that organic disease of the gastrointestinal tract can be identified in subsets of patients who fulfill the Rome criteria for IBS. Evidence for subtle inflammatory bowel disease, serotonin dysregulation, bacterial overgrowth and central dysregulation continue to accumulate. The underlying causes of IBS remain to be adequately identified, but IBS-PI is a clear-cut

entity. Furthermore, a genetic contribution to IBS also seems likely^[13].

Infection and Immune activation in IBS

There is increasing evidence regarding the role of immune activation in the etiology of IBS, which has mainly been shown in studies investigating mechanisms of IBS-PI^[19]. Approximately 1 in ten patients with IBS believe their IBS began with an infectious illness. Prospective studies have shown that 3%-36% of enteric infections lead to persistent new IBS symptoms; the precise incidence depends on the infecting organism. Whereas viral gastroenteritis seems to have only short-term effects, bacterial enteritis and protozoan and helminth infections are followed by prolonged IBS-PI. Risk factors for developing IBS-PI include, in order of importance, prolonged duration of initial illness, toxicity of infecting bacterial strain, smoking, mucosal markers of inflammation, female gender, depression, hypochondriasis, and adverse life events in the preceding 3 mo. Age older than 60 years might protect against IBS-PI, whereas treatment with antibiotics has been associated with increased risk. The mechanisms that cause IBS-PI are unknown but could include residual inflammation or persistent changes in mucosal immunocytes, enterochromaffin and mast cells, enteric nerves, and the gastrointestinal microbiota^[20]. Exposure to intestinal infection induces persistent low-grade systemic and mucosal inflammation, which is characterized by an altered population of circulating cells, mucosal infiltration of immune cells and increased production of various cytokines in IBS patients. Recent studies have also indicated an increased innate immune response in these patients by evaluating expression and activation of Toll-like receptors^[21]. These findings suggest that immune activation may play a crucial role in the pathogenesis of IBS. In addition, psychological stress has been reported to be one of the factors that induce immune activation. However, it remains unknown whether immune activation in IBS patients is largely dependent on infectious gastroenteritis and/or psychological stress. Additional studies are necessary to understand the precise mechanism of immune activation and its relationship to the development of IBS^[22].

Serotonin dysregulation

Serotonin (5-HT), acting particularly through the 5-HT₃ and 5-HT₄ receptors, plays a significant role in the control of gastrointestinal motility, sensation, and secretion^[23-25]. Furthermore, observations that plasma 5-HT concentrations are reduced in IBS patients with constipation^[25,26], but raised in those with diarrhea^[26,27], especially those showing postprandial symptoms^[27], provide further support for its involvement in the motor and sensory dysfunction associated with this condition. Thus there has been considerable interest in these receptors as possible therapeutic targets for IBS, with agonists at the 5-HT₄ receptor predicted to enhance gastrointestinal propulsion (that is, to be prokinetics)^[28-30] and antagonists at the

5-HT₃ receptor to slow gastrointestinal transit and reduce visceral sensation^[28,31-33].

Bacterial overgrowth

Studies indicate that small intestinal bacterial overgrowth (SIBO) is prevalent in IBS, it remains unclear whether SIBO causes IBS^[34]. Although, the bacterial overgrowth hypothesis of IBS may be biologically plausible, there is also a strong rationale for competing hypotheses. It is unlikely that SIBO is the predominant cause of IBS in all comers, because competing explanations are sensible and defensible. Moreover, data indicate that the test used to promulgate the SIBO hypothesis - the lactulose hydrogen breath test - may not have measured SIBO in the first place^[34]. We do not have evidence of SIBO being absent before IBS symptoms, and present after IBS emerges. There is not a dose-response relationship between small intestinal microbiota and IBS symptoms. The relationship between SIBO and IBS is highly inconsistent among studies. Many effective IBS therapies do not address SIBO at all, yet have a more favorable “number needed to treat” than antibiotics. IBS does not behave like a traditional infectious disease, suggesting that microbes may not principally cause the syndrome. Other factors may confound the relationship between SIBO and IBS, including proton pump inhibitors. Whereas the brain-gut hypothesis is evolutionarily sensible, the bacterial hypothesis is harder to defend from an evolutionary perspective. So it can be said that bacteria may contribute to some IBS symptoms, but that bacteria cannot be the only explanation, and a causal link between SIBO and IBS is not secure^[34].

Central dysregulation and brain-gut interaction

Psychosocial factors appear to be important in IBS, although whether these factors directly alter gastrointestinal function remains uncertain. It is also possible that gastrointestinal dysfunction modulates central processes too. For example, there is good evidence now that abuse in childhood or adulthood is associated with IBS, although whether it is of etiological importance remains in dispute^[35]. Anxiety and depression are also common in IBS^[7,14]. Some have conceptualized IBS as a somatization disorder, but the clear evidence for an organic pathophysiology in some cases of IBS makes this unlikely^[14,35].

The central nervous system modulates various functions such as secretion, motility, and blood flow^[36]. Signals from the gut, in turn, are involved in regulating reflexes. Perception of events in the gut involves activation of afferent pathways, with information being modulated at different levels, peripheral as well as central^[37]. A major advance in our understanding of brain-gut interaction and its alteration in IBS occurred with the introduction of functional magnetic resonance imaging. This technique allowed assessment of the difference in cortical function in response to gut stimulation between healthy subjects and IBS patients^[38], opening the door for potential pharmacologic and behavioral interventions.

There are differences in brain responses in patients with IBS that have been documented. For example, measures of regional cerebral blood flow during rectal distention have shown that IBS patients have greater activation of the anterior cingulate cortex, amygdala and dorsomedial frontal cortex, in contrast to patients with ulcerative colitis and controls^[39]. It has been postulated that the brains of people without IBS are better able to activate endogenous pain inhibition areas. This could represent a genetic predisposition to IBS. The antidepressant amitriptyline has been shown to reduce rectal pain and this has been correlated to activation of the right prefrontal cortex, right insula and perigenual anterior cingulate cortex^[40]. Such central changes might explain the potential benefit of antidepressants in IBS.

Genetics

Studies have suggested that there is a genetic contribution to IBS, although the importance of this remains in dispute^[41]. A search for candidate genes continues, with the working hypothesis that environmental factors likely play an important role in the pathogenesis in the genetically primed individual.

DIAGNOSIS AND CLINICAL MANIFESTATIONS

Diagnostic criteria have evolved since 1979 when Manning *et al*^[42] first published their criteria. The changes have included the Rome I criteria, which were revised to the Rome II guidelines^[13], and now to the most recent Rome III criteria to allow for ease of diagnosis. The Rome II criteria state that a patient must have abdominal pain or discomfort for at least 12 wk, which need not be consecutive, during the past 12 mo. This pain or discomfort must have at least two of the following three features: relief with defecation, association with a change in stool frequency, or association with a change in stool consistency. The Rome III diagnostic criteria simply state that a patient must have recurrent abdominal pain or discomfort at least 3 d/mo in the last 3 mo associated with two or more of the following features: improvement with defecation, onset associated with a change in stool frequency, or onset associated with a change in stool consistency^[3]. A 2009 position statement issued by the American College of Gastroenterology (ACG) states that no symptom-based criteria have ideal accuracy for diagnosing IBS^[43]. Therefore, the ACG Task Force defines IBS as abdominal pain or discomfort that occurs in association with altered bowel habits over a period of at least 3 mo. Understanding the pathogenesis of IBS is important because today's newer pharmacotherapy agents are beginning to target the known pathophysiologic mechanisms of IBS. Altered gastrointestinal motility, visceral hypersensitivity, post infectious reactivity, brain-gut interactions, alteration in fecal micro flora, bacterial overgrowth, food sensitivity, carbohydrate malabsorption, and intestinal inflammation all have been implicated in the

Table 1 Summary of diagnostic criteria used to define irritable bowel syndrome

Diagnostic criteria	Symptoms, signs, and laboratory investigations included in criteria
Manning (1978)	IBS is defined as the symptoms given below with no duration of symptoms described. The number of symptoms that need to be present to diagnose IBS is not reported in the paper, but a threshold of three positive is the most commonly used: Abdominal pain relieved by defecation More frequent stools with onset of pain Looser stools with onset of pain Mucus per rectum Feeling of incomplete emptying Patient-reported visible abdominal distension
Kruis (1984)	IBS is defined by a logistic regression model that describes the probability of IBS. Symptoms need to be present for more than two years. Symptoms: Abdominal pain, flatulence, or bowel irregularity Description of character and severity of abdominal pain Alternating constipation and diarrhea Signs that exclude IBS (each determined by the physician): Abnormal physical findings and/or history pathognomonic for any diagnosis other than IBS Erythrocyte sedimentation rate > 20 mm/2 h Leukocytosis > 10000/cc Anemia (Hemoglobin < 12 for women or < 14 for men) Impression by the physician that the patient has rectal bleeding
Rome I (1990)	Abdominal pain or discomfort relieved with defecation, or associated with a change in stool frequency or consistency, PLUS two or more of the following on at least 25% of occasions or days for 3 mo: Altered stool frequency Altered stool form Altered stool passage Passage of mucus Bloating or distension
Rome II (1999)	Abdominal discomfort or pain that has two of three features for 12 wk (need not be consecutive) in the last one year: Relieved with defecation Onset associated with a change in frequency of stool Onset associated with a change in form of stool
Rome III (2006)	Recurrent abdominal pain or discomfort three days per month in the last 3 mo associated with two or more of: Improvement with defecation Onset associated with a change in frequency of stool Onset associated with a change in form of stool

IBS: Irritable bowel syndrome; 5-HT: 5-hydroxytryptamine.

pathogenesis of IBS. However, the perceived symptoms from these mechanisms consist of abdominal pain or discomfort, bloating, diarrhea, and constipation. Historically, medical management has focused on symptomatic treatment of these individual complaints. In addition, our current pharmaceutical repertoire is usually limited to treatment for only one symptom.

As individual symptoms are not completely accurate in diagnosing IBS, criteria have been developed to identify a combination of symptoms to diagnose the condition. Manning *et al*^[42] promulgated the original account of this approach. Two of four studies that have evaluated the accuracy of the Manning criteria suggested they perform well, with a sensitivity of 78% and specificity of 72%. Kruis *et al*^[44] developed another set of criteria; three of four studies that examined the accuracy of the Kruis symptom score suggested it provides an excellent positive predictive value with a high sensitivity (77%) and specificity (89%). The Rome criteria subsequently were developed and have undergone three iterations. One study has evaluated the accuracy of Rome I criteria, and determined it had a sensitivity of 71% and specificity of 85%. Studies have demonstrated that there are no

consistent differences in sensitivity or specificity between Manning, Rome I, and Rome II and support the validity of symptom-based IBS criteria^[45]. A cross sectional study by Engsbro *et al*^[46] exploring the sensitivity of Rome III criteria in primary care in patients suspected of irritable bowel syndrome. In this study, a total of 604 patients were referred and 499 were included (32.8 ± 9.5 years, 75% were female). The Rome III criteria were fulfilled by 376 patients (sensitivity, 0.75; 95%CI: 71%-79%). Rome III-positive patients more frequently reported disturbed defecation, had a higher symptom burden, and lower disease-specific health-related quality of life compared with Rome III-negative patients. The various symptom-based criteria identified slightly different subpopulations with the highest agreement between the Rome II and III criteria^[46] (Table 1).

TREATMENTS

Before discussing treatment options with patients suspected of IBS, the physician should carefully perform a detailed history and physical to exclude other diagnoses with symptoms similar to those of IBS. The American

College of Gastroenterology Functional GI Disorders Task Force stated that the current data do not support extensive testing in IBS patients^[23]. IBS patients do not appear to have a higher prevalence of organic disease than the general population. If no alarming findings exist such as weight loss, hematochezia, iron deficiency, and symptoms that are typical of IBS, routine diagnostic testing is not recommended. If symptoms are not typical or alarm features are present, testing should include complete blood cell count, comprehensive metabolic profile, an inflammatory marker such as erythrocyte sedimentation rate or C-reactive protein, and thyroid stimulating hormone level. If diarrhea is predominating, fecal leukocytes and stool analysis for *Clostridium difficile* when appropriate (such as patients with antibiotic use within 3 mo or recent chemotherapy) should be obtained. Travel and social history may make stool tests for Giardia and Cryptosporidium antigens appropriate. Serology for celiac disease, preferably the tissue transglutaminase or TTG-IgA, should be performed as part of the workup for all patients suspected of having IBS associated with diarrhea or mixed subtype. Sanders *et al*^[47] demonstrated that a higher prevalence of celiac disease exists in IBS patients (4.67%) compared with the general population (< 1%). However, a recently published study found that 1.7% of IBS patients were positive for TTG, and this was not different from the placebo group^[48]. Nonetheless, testing for celiac disease does seem reasonable in non constipating IBS. Colonoscopy is acceptable in patients with a family history of inflammatory bowel disease; colon cancer; alarm symptoms, such as hematochezia, nocturnal or progressive abdominal pain, weight loss, anemia, elevated inflammatory markers, or electrolyte disturbances; or in patients over 50. When a colonoscopy is performed in patients with IBS-D, random biopsies should be performed to rule out microscopic colitis. These are general suggestions, as each individual patient will present with unique characteristics. The physician must realize that a strong physician-patient relationship will be the foundation for effective treatment and realistic expectations^[3]. Many patients with IBS have been bounced around the medical field for many years with varying diagnoses because of the lack of interest or profound frustration by the physician in treating IBS, possible stigma of this disease as being a psychiatric entity, or lack of clinical, physical, or laboratory diagnostic criteria. The medical literature supports gaining the confidence of the patient on the first clinical interview through attentive listening, and detailed explanations of the pathophysiology, natural history, management, and prognosis of IBS^[49,50]. Responding to all the patient's concerns and questions and spending time in the initial visit validates their problem. This reassurance aids in the patient's attempts to understand and accept his or her affliction. Setting appropriate goals and limits gives patients a more structured environment and a sense of purpose and allows them to participate in their own health care strategy^[3]. Once a rapport with the patient has been established, long-term goals for this chronic illness are easier to obtain as evident by a decrease in

the number of health care visits, reduction in symptoms, and improved patient satisfaction^[3]. The physician should also emphasize the chronic nature of this syndrome because nearly 75% of patients continue to have a diagnosis of IBS 5 years later^[51].

Non-pharmacological therapies

A complementary and alternate medicine (CAM) is often used for chronic medical conditions, health promotion, and/or disease prevention^[52]. Currently available systematic reviews provide conflicting findings about the effectiveness of CAM therapies for IBS. The American College of Gastroenterology Task Force on IBS^[3] reported that CAM therapies have not demonstrated any strong evidence-based support for positive outcomes. Other systematic reviews, however, indicate evidence of effectiveness^[53]. Among mind-body therapies, hypnotherapy and cognitive-behavioral therapy seem to be the most widely accepted by IBS patients. Relaxation techniques have been studied for their potential role in alleviating IBS symptoms. Multiple studies have indicated positive correlations among psychological distress, daily stress, and GI symptom aggravation^[54-57] that triggered IBS symptoms^[58]. Women with IBS tend to report a higher amount of psychological distress and lifetime psychopathology than those with no GI symptoms^[58]. Relaxation training may be beneficial for symptom improvement and appears to be at least as effective as standard pharmacological treatment. Acupuncture can cause physiological changes that affect various endogenous neurotransmitter systems. Of specific interest to the treatment of IBS is the influence of acupuncture and moxibustion on the serotonergic and cholinergic neurotransmission of the brain-gut axis. Both animal and human trials indicate specific targets for acupuncture on serotonergic, cholinergic, and glutamatergic pathways as well as reductions in blood cortisol levels^[59-63].

EXERCISE

Exercise can help maintain GI function and reduce stress, which can help relieve some IBS symptoms. Studies of IBS indicate positive relationships between physical activity and symptom relief^[64]. Physical activity, such as pedaling a bicycle, protects against GI symptom aggravation and alleviates gas in several studies^[64-66]. The practice of yoga has also demonstrated reduction of IBS symptoms in both adult and adolescent populations^[67,68]. Pranayama yoga has been identified as an exercise regimen that increases sympathetic tone, which is decreased in IBS-D patients^[69]. In a two-month study, a yoga intervention group practiced twice daily, while the conventional treatment group received 2-6 mg loperamide daily. Results indicated that yoga demonstrated improvement of IBS symptoms equivalent to conventional treatment^[69].

DIET MODIFICATION

A primary goal of all IBS interventions is to provide the

patient with relief of symptoms and improve the quality of life. Although the data from clinical trials may in some cases not provide strong evidence for benefits of dietary modification, it remains the primary non-pharmacological clinical intervention for IBS patients; exclusion diets are successfully used by many clinical practitioners^[3]. Food intolerances or allergies are strong contributors to the exacerbation of IBS symptoms. Individuals with IBS often discover that certain foods aggravate symptoms^[70-72], while others have found relief from IBS symptoms by modifying their daily diet and increasing exercise activities^[73-75]. Symptoms of IBS may be associated with visceral hyperactivity, GI motility disturbances, sugar malabsorption, gas-handling disturbances, and abnormal intestinal permeability^[1,76]. Elimination diets are often employed that remove the most common allergens from the diet^[77]. Although some patients reported that removing wheat, dairy products, eggs, coffee, yeast, potatoes, and citrus fruits from their diets is helpful, such restrictions may be difficult to follow^[72]. Dietary restrictions may provide patients with relief of IBS symptoms over time, while entirely skipping meals has been found to worsen IBS symptoms^[65,72].

MACRONUTRIENTS: FAT, SUGAR, AND SUGAR ALCOHOLS

IBS studies indicate a positive relationship between fat intake and increased stool number and diarrhea. Intake of carbohydrates can also aggravate IBS symptoms^[72]. Offending carbohydrates include fermentable oligo-, di-, and monosaccharides and polyols (FODMAPs). This group includes fructans, galactans, lactose, fructose, sorbitol, xylitol, and mannitol^[78]. Sorbitol and other sugar-alcohols found in most sugar-free or reduced-sugar products are poorly absorbed in the GI tract and may cause increased flatulence, abdominal discomfort. Other types of sugar-alcohols proposed to aggravate IBS symptoms include mannitol, xylitol, erythritol, lactitol, maltitol, and isomalt^[71]. Due to the multitude of variables related to IBS symptoms, study results are difficult to validate and challenging to interpret.

FIBER

Fiber intake from fruits and vegetables is inversely correlated to bloating^[74]. The addition of psyllium fiber, especially for persons with IBS-C, reduced IBS symptoms in some people^[71,79,80] while either wheat bran or a low-fiber diet was found to be an ineffective management measure as evaluated by two meta-analyses of a total of 30 studies^[80]. Because most of the evaluated studies had small sample sizes, the results are highly variable. Other widely variable factors included the amount of soluble (5-30 g) and insoluble (4.1-36 g) fiber added to the diet and the duration of study intervention (3-16 wk). Overall, consumption of soluble fiber resulted in a decrease in global IBS symptoms and constipation, whereas insoluble fiber

demonstrated a less significant effect. Neither intervention, however, decreased abdominal pain in IBS patients. Due to its moderate effectiveness, additional intake of soluble fiber may be recommended for IBS-C patients. Studies also revealed that pain relief was not associated with increased fiber intake and that the addition of insoluble fiber such as nuts or whole grains to the diet had either no effect or exacerbated IBS symptoms^[79].

LACTOSE INTOLERANCE

Patients with IBS were found to have significantly more subjective lactose intolerance complaints (bloating, distention, and diarrhea) than those without IBS and to have increased likelihood of lactose malabsorption than the general population^[81]. Thus, decreased intake of lactose can benefit some IBS patients^[82]. It is hypothesized that, following ingestion of lactose, hydrogen gas is produced and gut distention is promoted due to bacterial fermentation of the unabsorbed lactose. Interestingly, the majority of IBS sufferers, however, failed to test positive for hydrogen breath tests that indicate lactose intolerance^[82].

PHARMACOTHERAPY

In the past patients with IBS were treated by giving medicines targeting individual symptoms of IBS such as bloating, abdominal pain, diarrhea, and constipation. However, newer medications are beginning to focus on the molecular level like serotonin receptor agonists and antagonists and drugs that act locally on chloride channels (Lubiprostone) and guanylate cyclase receptors (linaclotide) in the gastrointestinal tract^[83]. The problem is that no one drug fits all, meaning that the IBS population is very diverse with each individual presenting with different prevailing complaints. The heterogeneity of the IBS population exists because of the wide range of complaints and the varying degree of symptom severity. Because of poorly designed studies and ill-defined outcomes, the medical literature regarding IBS therapy is generally inconsistent^[84,85]. The placebo response in IBS patients is quite significant with short-term trials reporting a 30%-80% response^[86]. One can imagine the difficulty of treating a syndrome that is heterogeneous in its presentation, lacks in significant supporting medical literature, and has a remarkably high placebo response rate. Even though patients' symptoms overlap, addressing them individually allows the physician to simplify and organize the appropriate medical therapy.

ABDOMINAL PAIN

The major contributing factor in abdominal pain experienced by IBS patients is visceral hypersensitivity. The management of abdominal pain in IBS has changed very little over the past few decades: antispasmodics remain a cornerstone of therapy. Antispasmodic agents work by anticholinergic properties like dicyclomine and hyoscya-

mine. The evidence of the effectiveness of these agents is not compelling, as even the meta-analyses for smooth muscle relaxants are conflicting. One meta-analysis demonstrated an advantage over placebo for antispasmodics in terms of abdominal pain and distention^[87]. Brandt *et al*^[43] examined 18 randomized controlled trials, of which only three included dicyclomine and hyoscyamine, but concluded the trials were of suboptimal quality based on study design with inadequate duration of treatment. With only one of those previously mentioned three studies demonstrating a statistically significant improvement in global IBS symptoms and abdominal pain^[88] and more frequent anticholinergic side effects versus placebo (69% *vs* 16%), it is easy to understand why insufficient data exist about antispasmodics. Even though the antispasmodic medications have not demonstrated an overwhelming statistically significant advantage^[84], it is common practice in the United States to utilize these agents. The anticholinergic effects, including constipation, dry mouth, visual disturbances, and urinary retention, can lead to discontinuation of these medications. These medications can be given as an oral formulation or a sublingual tablet, and be dosed on an as-needed or regular basis. Many patients benefit by taking the medication before meals. If known exacerbating factors such as a particular diet or stress are anticipated, these medications can be given as a prophylactic measure. It has also been noted that medicines such as dicyclomine can lose effectiveness with chronic use; therefore, it may be best employed on an as-needed basis^[7]. Given the potential side effect of constipation, these medications should be used cautiously in IBS with constipation predominating^[43].

EFFECTIVENESS OF ANTIDEPRESSANT AGENTS IN THE MANAGEMENT OF IRRITABLE BOWEL SYNDROME

Tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs) are more effective than placebo at relieving global IBS symptoms, and appear to reduce abdominal pain. There are limited data on the safety and tolerability of these agents in patients with IBS. Nine trials were identified that tested TCAs in various doses for IBS. TCAs clearly were superior to placebo (NNT = 4, 95%CI: 3-6)^[43]. There is no convincing evidence that the dose needed has to be in the antidepressant range, and most trials tested low-dose TCAs. In two of the trials, abdominal pain was the primary endpoint and a significant benefit was observed. Five trials that assessed SSRIs also showed a benefit in IBS over placebo (NNT = 3.5)^[43]. Theoretically, SSRIs should be of most benefit for IBS-C, whereas TCAs should be of greatest benefit for IBS-D because of their differential effects on intestinal transit time, but there is a lack of available data from the clinical trials to assess this clinical impression. The safety of using antidepressants in IBS remains poorly documented, although data suggest that the SSRIs are tolerated better than the TCAs. No data on the efficacy of SSRIs or

other new antidepressant drug classes are available in the literature^[43].

When addressing abdominal pain in the IBS patient, it is helpful to distinguish whether the pain is constant/chronic versus intermittent with known exacerbating factors. The latter has better results when treated with the antispasmodics, whereas the former may have a better response from low-dose TCAs or SSRIs^[3]. Antidepressants in IBS patients can facilitate endogenous endorphin release, blockade of norepinephrine leading to enhancement of descending inhibitory pain pathways, and blockade of the pain neuromodulator, serotonin^[89,90]. TCAs, *via* their anticholinergic properties, also slow intestinal transit time, which may provide benefit in diarrhea-predominant IBS^[91]. The goal is to reduce the visceral hypersensitivity, allowing for better management of chronic pain. Reducing abdominal pain allows for reduced anxiety and a distraction from these patients' IBS complaints^[43]. A 2009 meta-analysis concluded that antidepressants were significantly more effective than placebo for the relief of pain and global symptoms. The treatment effects were similar for SSRIs and TCAs^[92]. Some patients will hesitate to use antidepressants because of the associated stigma of these medications; therefore, the management of chronic pain should be emphasized. Counseling the patient regarding the potential side effects of constipation and sedation is essential, and caution should be used when prescribing these medications in constipation predominant IBS^[43]. Treatment with TCAs generally starts with a very low dose given before bedtime and even with gradual increases never reaches the same doses that are used to treat depression. Often only 25-50 mg of amitriptyline can be utilized with success, although one can start with a very low dose of 10 mg daily. Currently, the evidence for using SSRIs is limited and inconsistent. These agents may be more beneficial in treating patients with concomitant anxiety and constipation-predominating IBS; generally, there are fewer side effects.

Bloating

Bloating is unfortunately a very subjective complaint among IBS patients and remains extremely difficult to treat. The majority of the medications designed for this indication have not been helpful. Simethicone and activated charcoal theoretically should aid in alleviating bloating, but have not demonstrated a true clinical or even statistical benefit. The role of prokinetic agents has yet to be defined and further well-designed studies are needed^[86]. Because even IBS treatments such as dietary fiber supplementation can actually worsen bloating secondary to colonic metabolism of non digestible fiber, care must be taken in prescribing fiber in patients with a significant bloating problem^[86,93]. Non absorbable sugars like lactulose potentially used for constipation predominating patients can exacerbate gaseous distention. The physician should instruct the patient to be mindful of gaseous food (*i.e.*, beans, carbonated beverages, *etc.*) and attempt to elicit any aerophagia symptoms.

Constipation

When treating mild to moderate symptoms of constipation-predominant IBS, dietary and lifestyle modifications should be the initial management tools. Patients should increase their consumption of fiber-enriched foods, and the physician needs to encourage fluid intake to prevent stool dehydration. Teaching the patient to schedule times for bowel evacuations with the aid of stimulating substances such as coffee or prunes allows for a regimental routine, thus eliminating previously unrecognizable bad habits. Bulking agents (corn fiber, bran, psyllium, polycarbophil, ispaghula husk, and methylcellulose) are a simple and inexpensive next-treatment option. In theory, adding these to the diet increases luminal water, which adds bulk to the stool and allows easier stool passage. One meta-analysis of 13 trials using bulking agents concluded that evidence was lacking to firmly demonstrate an advantage with only polycarbophil and ispaghula husk in three trials exhibiting improvement in constipation^[84]. Not surprisingly, no benefit was seen with abdominal pain or bloating. Furthermore, a systematic review summarized that all 13 trials were flawed in methodology and fiber was no more effective than placebo^[94]. A randomized placebo controlled trial compared the effectiveness of increasing dietary content of soluble fiber (psyllium) or insoluble fiber (bran) in patients with IBS^[95]. It was concluded that those patients taking psyllium had a significant improvement in relief of symptoms and overall reduction in severity of symptoms. However, bran showed no clinical benefit and actually caused worsening of symptoms in many cases^[93]. Given that these agents possess a relatively safe profile, it is reasonable to prescribe a trial as initial management for constipation with the understanding that these agents can worsen bloating and abdominal discomfort. Currently, there are no randomized controlled trials examining laxatives in IBS patients^[43]. However, polyethylene glycol can be considered for refractory cases as it was shown to improve stool frequency but not abdominal pain^[86].

Lubiprostone is a locally acting chloride channel activator that enhances chloride-rich intestinal fluid secretion. It was initially approved for use in chronic idiopathic constipation, but later received approval for use in women with constipation-predominant IBS. Two placebo-controlled trials as well as an open-label study showed significant overall response to the medication^[96]. The approved dose for IBS is 8 µg twice daily, and 24 µg dosing can be used for constipation. There seem to be no short-term safety issues and the main side effect is nausea. However, long-term safety remains to be established. Further studies will need to be performed to determine its role in treatment of male IBS patients. Currently, it is best reserved for women with IBS and severe constipation that has been refractory to other treatments.

Diarrhea

When considering treatment for IBS-D, the physician should attempt to elicit any particular stressors that might initiate the patient's exaggerated gastro colic reflex. The

anecdotal event could include eating, walking, traveling with the fear of not being near a restroom, or stressful encounters in a social setting or even at work. As previously mentioned, keeping a diary of not only foods but also events or situations that correlate with the onset of diarrhea can help the patient in recognizing these stressors and allow the physician to better coordinate therapy. Once these predictable episodes of diarrhea are known, the physician can begin to utilize conservative, first-line treatment with anti diarrhea agents. Of the two most commonly used anti diarrhea agents, loperamide and diphenoxylate HCl-atropine, loperamide is the only one to have been studied for IBS-D. These medications increase gastrointestinal transit time by interacting with the GI musculature, thus allowing for more water absorption^[86]. Of the few randomized controlled trials, the data indicated a decrease in diarrhea without any effect on global IBS symptoms or abdominal pain^[94]. The physician should instruct the patient to discontinue these medications once the diarrhea has subsided to prevent constipation. Because of this side effect, the physician should have a higher threshold in prescribing these agents in IBS patients with alternating diarrhea and constipation^[43]. Although opioid medications can decrease diarrhea, they should be used with extreme caution because of the possibility of severe constipation and obviously for the addiction potential. As a result, most physicians avoid using these agents. Cholestyramine may have a role in the treatment of diarrhea-predominant IBS, but further evidence is needed to better elucidate the role of bile acid malabsorption and its treatment in IBS^[86]. Cholestyramine's side effect of constipation should be remembered. As mentioned above, patients with multiple IBS symptoms that include abdominal pain and diarrhea may benefit from low dose TCAs, which decrease the frequency of bowel movements and treat the visceral hypersensitivity. Alosetron is a 5-hydroxytryptamine (serotonin) 3-receptor antagonist, which modulates visceral afferent activity from the gastrointestinal tract^[96]. A meta-analysis that included multiple randomized controlled trials demonstrated its efficacy in relieving global IBS symptoms. These trials demonstrated effectiveness versus placebo for improvement of abdominal discomfort, stool frequency, consistency, and urgency^[10,97]. It has been found to be most effective in women with IBS-D. Constipation was reported in approximately one third of patients using alosetron^[10,97]. Severe constipation and ischemic colitis were rarely reported as well as some potential drug-related fatalities^[86,97]. After being withdrawn from the market, it was reapproved by the United States Food Drug Administration with restrictive guidelines^[7], and is currently available under a specific prescribing protocol, with a starting dose of 1 mg daily.

MISCELLANEOUS TREATMENT STRATEGIES

One of the interesting approaches is the utilization of

antibiotics in IBS patients with SIBO. A study by Pimentel *et al*^[98] found that out of 202 IBS patients, 157 or 75% had abnormal lactulose hydrogen breath test results signifying bacterial overgrowth. However, the study did show that patients with successful eradication had statistically significant improvement in abdominal pain and diarrhea. The same author subsequently published a double-blinded randomized controlled trial substantiating that the normalization of the lactulose breath test with antibiotics in IBS patients led to a significant reduction of IBS symptoms^[99]. In the TARGET 1 and TARGET 2 trials, patients with IBS and without constipation were randomly assigned to receive either rifaximin 550 mg three times a day or a placebo for 2 wk. In this study, results showed that those patients that received rifaximin were more likely to report relief of global IBS symptoms than those that received a placebo^[100]. These were large studies enrolling over 1200 patients with greater than 70% completing the study which followed the patients for 12 wk after treatment. Like most IBS studies, there was a predictable response in the placebo group. Currently, there are insufficient data to recommend breath testing for SIBO in all IBS patients as the optimal test is unclear. It is also not clear why antibiotics are effective—are they treating small bowel bacterial overgrowth or altering the colonic flora? The benefit from treatment appears to be transient. Therefore, the routine use of antibiotics in all IBS patients is not recommended. However, it is reasonable to try a 2-wk trial of rifaximin in those patients with IBS without constipation and with moderate to severe symptoms, especially bloating, who have failed other therapies. In prior studies, there were no significant side effects of rifaximin compared with placebo, but currently its cost can be a prohibitive factor.

ALTERNATIVE THERAPIES FOR IRRITABLE BOWEL SYNDROME

Many IBS patients turn to herbal preparations because of a widespread perception that they are safe and effective for a variety of ailments. Although many patients utilize herbal and alternative approaches, they usually do not volunteer this information during the physician interview, so it is important to specifically ask about these agents in a nonjudgmental fashion. An excellent review by Spanier *et al*^[101] examined these alternative therapies. Though unstudied in IBS, aloe has been frequently used in treating constipation-predominant IBS. Peppermint oil, which has antispasmodic properties by relaxing smooth muscle, demonstrated efficacy in terms of abdominal discomfort and pain and abdominal distention in IBS patients in three randomized trials when compared with placebo^[102,103]. The American College of Gastroenterology Task Force on IBS determined that antispasmodics, such as peppermint oil, may provide short-term relief, but evidence for long-term efficacy is not available and evidence for safety and tolerability is limited^[43]. Perhaps the most common strategy employed by patients is to alter the

native flora of the colon with “probiotics” such as the commercially available preparations of the *Lactobacillus* species^[84,101]. Patients have often tried these preparations even before seeking medical care due to widespread marketing techniques and availability. Trials to date remain conflicting and no clear benefit has yet to be established for lactobacilli. However, *Bifidobacteria*, *Saccharomyces boulardii* and other combinations of probiotics demonstrate some efficacy. The probiotic strain *Bifido bacterium infantis* 35624 (one capsule per day) has been shown to reduce pain, bloating, and defecatory difficulty and to normalize stool habit in IBS patients, regardless of predominant bowel habit^[104]. The probiotic strain *Bifido bacterium lactis* DN-173 010 has been shown to accelerate gastrointestinal transit and to increase stool frequency among IBS patients with constipation^[53]. However, a systematic review of randomized clinical trials evaluating the efficacy, safety, and tolerability of probiotics in IBS determined that only *Bifido bacterium infantis* 35624 showed significant improvement in global and specific IBS symptoms in appropriately designed studies^[104]. The theory behind the mechanism for improvement appeared to be downregulation of a proinflammatory state. No other probiotic showed significant improvement in IBS symptoms in an appropriately designed study^[104]. The best clinical evidence for probiotic efficacy is in protection against infection, especially in neonatal and elderly groups. The role of probiotics in IBS remains uncertain given the limited clinical studies^[104]. The role of psychological therapies has been analyzed in multiple studies^[105]. The methodological design of most of these studies was inadequate; therefore, unequivocal evidence is lacking. However, the ACG Task Force concluded that cognitive therapy, dynamic psychotherapy, and hypnotherapy are more effective than usual care in relieving global symptoms of IBS^[43]. Along the lines of alternative therapy, many patients will seek methods considered nontraditional in Western medicine. This is not surprising given the frustration of the symptoms. Individual patients may obtain relief from acupuncture, meditation, and relaxation techniques. There has been a recent study showing the effectiveness of mindfulness-based stress reduction in a small number of patients^[105].

TREATMENT OF NONGASTROINTESTINAL SYMPTOMS

The IBS patient population has a wide variety of other symptoms. A study by Gralnek *et al*^[106] of the health-related quality of life (HRQOL) of IBS showed significant other symptomatology. Patients with IBS had lower scores on the SF 36^[107], a QOL scale. This was specifically noted in areas such as bodily pain, emotional well-being, fatigue, and poor social functioning. It is recommended that clinicians perform routine screening for diminished HRQOL in their IBS patients^[94]. Bringing a treatment strategy into play that addresses these other mental and physical symptoms is difficult; again, the rela-

Table 2 Emerging therapies for irritable bowel syndrome

Agent	Mechanism of action	Targeted disorder	Clinical status
Peripheral acting agents			
Crofelemer	CFTR inhibitor	IBS-D	Phase 2b complete
Linaclotide (MD-1100)	Guanylatecyclase-c agonist	IBS-C	Approved by US FDA in 2012, 30 th August
Arverapamil (AGI-003)	Calcium channel blocker	IBS-D	Phase 3
Verapamil	Kappa opioid agonist	IBS	Phase 2b complete
Mitemincinal	Motilin receptor agonist	IBS-C	Phase 2
Peripheral and central acting agents			
Ramosetron	5-HT 3 antagonist	IBS-D	Phase 3
TD-5108	5-HT 4 agonist	IBS-C	Phase 2
DDP-773	5-HT 3 agonist	IBS-C	Phase 2
BMS-562086	Corticotropin-releasing hormone antagonist	IBS-D	Phase 2
GW876008	(319) Corticotropin-releasing hormone antagonist	IBS	Phase 2
DDP-225	5-HT 3 antagonist and NE reuptake inhibition	IBS-D	Phase 2
GTP-010	Glucagon-like peptide	IBS pain	Phase 2
AGN-203818	Alpha receptor agonist	IBS pain	Phase 2
Solabegron	Beta-3 receptor agonist	IBS	Phase 2
Espindolol (AGI-011)	Beta receptor antagonist	IBS (all subtypes)	Phase 2
Dextofisopam	2,3 benzodiazepine receptors	IBS-D and IBS-M	Phase 3

IBS-C: Irritable bowel syndrome with constipation; IBS-D: Irritable bowel syndrome with diarrhea; IBS-M: Mixed irritable bowel syndrome; CFTR: Cystic fibrosis transmembrane conductance regulator; US FDA: United States Food and Drug Administration.

relationship and rapport between the physician and patient is very important.

EMERGING THERAPIES FOR IBS

Our current knowledge on the pathogenesis of IBS has led to the identification of a wide variety of novel agents targeting various mechanisms, now in various stages of development. This discussion will focus on drugs that have progressed beyond the proof of concept stage of development and will consider agents with predominantly peripheral effects, as well as those with both peripheral and central effects. Table 2 summarizes the status of various centrally and peripherally acting agents which are under various stages of clinical trial (Table 2).

CONCLUSION

IBS is a common disorder characterized by abdominal pain and altered bowel habit for at least 3 mo. A 2009 position statement issued by the ACG states that no symptom-based criteria have ideal accuracy for diagnosing IBS. Therefore, the ACG Task Force defines IBS as abdominal pain or discomfort that occurs in association with altered bowel habits over a period of at least 3 mo. The Task Force recommends that further investigations are unnecessary in young patients without alarming features with the exception of celiac sprue serology, which may be of benefit in some patients. Further investigation such as colonoscopy is recommended in those over 50 years of age and in patients with alarming features. Trials suggest psyllium fiber, certain antispasmodics, and peppermint oil are effective in IBS patients although the quality of the evidence is poor. Evidence suggests that some probiotics may be effective in reducing overall IBS symptoms but more data are needed. Anti diarrheals reduce the frequency of stools but do not affect the overall

symptoms of IBS. 5HT 3 antagonists are efficacious in IBS patients with diarrhea and the quality of evidence is good. Patients need to be carefully selected, however, because of the risk of ischemic colitis. 5HT 4 agonists are modestly effective in IBS patients with constipation and the quality of evidence is good although the possible risk of cardiovascular events associated with these agents may limit their utility. Tricyclic antidepressants and selective serotonin reuptake inhibitors have been shown to be effective in IBS patients of all subtypes. The trials generally are of good quality but the limited number of patients included in trials implies that further evidence could change the confidence in the estimate of effect and therefore the quality of evidence was graded as moderate. Non absorbable antibiotics are effective particularly in IBS-D and selective C-2 chloride channel activators are efficacious in IBS-C with a moderate quality of evidence. Psychological therapies may also provide benefit to IBS patients although the quality of evidence is poor. Patients with IBS often seek CAM therapies, including cognitive-behavioral therapy, herbal therapies, probiotics, mind-body therapies, acupuncture, dietary changes, and exercise. Although most CAM therapies seem to provide some benefit in alleviating IBS, it is apparent that the duration, dosages, and specifics of the intervention greatly affect the outcomes. More studies need to be conducted to establish the subtle nuances associated with these treatments (*e.g.*, specific probiotics, standardization of herbal extracts, yoga style, *etc.*) to provide the most significant benefit for IBS. A wide variety of novel agents targeting various mechanisms of IBS are now in various stages of drug development.

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