Irritable Bowel Syndrome

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- Read the enclosed course.
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Faculty

Mark Rose, BS, MA, LP, is a licensed psychologist in the State of Minnesota with a private consulting practice and a medical research analyst with a biomedical communications firm. Earlier healthcare technology assessment work led to medical device and pharmaceutical sector experience in new product development involving cancer ablative devices and pain therapeutics. Along with substantial experience in addiction research, Mr. Rose has contributed to the authorship of numerous papers on CNS, oncology, and other medical disorders. He is the lead author of papers published in peer-reviewed addiction, psychiatry, and pain medicine journals and has written books on prescription opioids and alcoholism published by the Hazelden Foundation. He also serves as an Expert Advisor and Expert Witness to law firms that represent disability claimants or criminal defendants on cases related to chronic pain, psychiatric/substance use disorders, and acute pharmacologic/toxicologic effects. Mr. Rose is on the Board of Directors of the Minneapolis-based International Institute of Anti-Aging Medicine and is a member of several professional organizations.

Faculty Disclosure

Contributing faculty, Mark Rose, BS, MA, LP, has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

Division Planners

John V. Jurica, MD, MPH
Jane C. Norman, RN, MSN, CNE, PhD

Director of Development and Academic Affairs

Sarah Campbell

Division Planners/Director Disclosure

The division planners and director have disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

Audience

This course is designed for physicians, physician assistants, nurses, and other healthcare providers who may improve the identification and care of patients with irritable bowel syndrome.

Accreditations & Approvals

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Special Approvals

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Disclosure Statement

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Course Objective

The purpose of this course is to provide primary care physicians and nurses a review of irritable bowel syndrome, emphasizing pathophysiology, clinical assessment, and principles of care that take into account the biopsychosocial features of this common disorder. The goal is to improve clinical recognition and treatment and to promote management strategies that lead to better patient outcomes.

Learning Objectives

Upon completion of this course, you should be able to:

1. Describe the incidence and prevalence of irritable bowel syndrome (IBS).
2. Identify conditions that are commonly comorbid with IBS.
3. Outline the natural history and disease burden of IBS.
4. Review the pathogenesis and pathophysiology of IBS.
5. Discuss risk factors for the development of IBS and underlying etiology.
6. Describe the assessment of patients with suspected IBS, including presenting signs and symptoms, testing, and clinical diagnostic criteria.
7. Identify conditions that should be included in the differential diagnosis of IBS.
8. Discuss the role of laboratory studies and alarm features in reaching a diagnosis of IBS.
9. Evaluate the role of nonpharmacologic therapies for the treatment of IBS.
10. Compare and contrast available pharmacotherapies for the treatment of the various IBS subtypes.

EVIDENCE-BASED PRACTICE RECOMMENDATION

Sections marked with this symbol include evidence-based practice recommendations. The level of evidence and/or strength of recommendation, as provided by the evidence-based source, are also included so you may determine the validity or relevance of the information. These sections may be used in conjunction with the course material for better application to your daily practice.

INTRODUCTION

Until recently, irritable bowel syndrome (IBS) was considered a diagnosis of exclusion. The pathophysiology was poorly understood, patient outcomes were usually unsatisfactory, and clinicians considered IBS difficult and frustrating to manage [1]. The conceptual and empirical framework to inform the clinical care of patients with IBS took a large step forward in 2016, when the Rome Foundation published the Rome IV diagnostic criteria for IBS. These criteria incorporate the many scientific and clinical advances made since the release of the previous version (Rome III) in 2006. This was part of a larger project to overhaul and update scientific advances and clinical guidance to optimize the diagnosis and treatment of functional gastrointestinal (GI) disorders [2]. In addition, 18 review papers that detail the latest understanding of functional GI disorders were published by members of the Rome Foundation in 2016.

IBS is characterized by recurrent abdominal pain associated with disordered bowel habits (constipation, diarrhea, or a mix of constipation and diarrhea); abdominal bloating/distention is typically present. The symptoms must not have a definable organic, metabolic, or drug-induced basis [3]. IBS and other functional GI disorders are now understood as disorders of the gut-brain axis that arise through complex, bidirectional interactions of biopsychosocial factors.

EPIDEMIOLOGY

INCIDENCE AND PREVALENCE

IBS often has an insidious onset with intermittent exacerbation of symptoms so nonspecific and familiar that patients frequently do not feel a need to seek medical attention. As a result, there is often a significant lag period between onset, first physician visit, and the eventual IBS diagnosis, which renders the true incidence and prevalence of IBS difficult to establish [4]. An accurate measure of IBS prevalence is further complicated by differences in criteria used in epidemiologic studies. The first global study of functional gastrointestinal disorders found that IBS is less than half as prevalent using the Rome IV diagnostic criteria compared with Rome III [213]. The current ROME IV diagnostic criteria are more stringent, requiring the presence of abdominal pain at least weekly (discomfort not included), whereas ROME III required abdominal pain or discomfort no more often than two to three times monthly.

General Population

IBS affects persons regardless of age and biological sex but is most common in women and younger individuals. The worldwide prevalence of IBS among adults is between 4.1% (Rome IV criteria) and 10.1% (Rome III criteria) [213]. A population-based survey among 5,931 adults found that prevalence values (4.4% to 4.8%) of IBS (Rome IV criteria) are similar in the United States, Canada, and United Kingdom [214]. The estimated lifetime prevalence of IBS in adult North American and European populations is 10% to 20%, but only 5% to 7% have been diagnosed. IBS shows highest prevalence in South America (21%) and lowest prevalence in Southeast Asia (7%) [5; 6].

Clinical Populations

IBS is among the most common diagnosed GI disorders, accounting for 41% of patients with functional GI symptoms [5; 6; 7]. Among clinical populations, IBS accounts for 12% of all patients seen in primary care and 28% in gastroenterology clinics [7]. In the United States, patients with IBS are evenly distributed among three common presenting clinical patterns: IBS with diarrhea (IBS-D), IBS with constipation (IBS-C), and mixed IBS (IBS-M); in Europe, most patients reportedly have either IBS-C or IBS-M [5; 6].

Of all persons with IBS symptoms, only a minority seek primary care medical attention, estimated at 10% to 70% in European countries and around 30% in the United States. In a 2017 online survey of 1,924 participants with a history of gastrointestinal symptoms, 43% of individuals who met the criteria for IBS-D had not received a formal diagnosis of the disorder [9]. Patients with IBS-D tend to seek medical attention at higher rates than those with IBS-C

or IBS-M. Those seeking medical care report greater levels of pain and anxiety and greater impact on quality of life. In contrast, GI symptom severity does not differ greatly between the two groups [4; 8; 10].

Sex

The global prevalence of IBS is 14% in women and 8.9% in men, meaning the rate is 67% higher among women than men. This difference in reported sex-specific prevalence may be influenced in part by stigma associated with the diagnosis or by differing attitudes and behaviors that influence the decision to seek medical care rather than merely a variation in susceptibility or severity of underlying pathology [4; 11]. An alternative possibility is that regulatory mechanisms of the brain-gut axis may be more sensitive to fluctuations in female hormone physiology, promoting alterations that result in IBS pathophysiology [12].

In the United States, Canada, and Israel, IBS symptoms are 1.5 to 2 times more prevalent in women than men, while the female/male distribution is closer to even in Asia. Abdominal pain and constipation are more common symptom complaints in women, with diarrhea more common in men [5; 11].

Age

A meta-analysis of 81 epidemiologic studies found that IBS prevalence decreases with age. The prevalence rate in patients younger than 40 years of age is 11.0%, with decreased rates in each subsequent decade (9.6% for persons in their 40s, 7.8% for persons in their 50s, and 7.3% for persons in their 60s). The lowest IBS prevalence rates are among persons 50 years of age and older [13; 14].

Challenges to Obtaining Accurate IBS Epidemiology Data

Prevalence estimates for IBS are impacted by stigma associated with seeking health care for IBS symptoms or receiving a functional GI disorder diagnosis. Lower reported prevalence is likely in areas where greater stigma is perceived or where symptoms are so common as to be viewed as variations of normal. For example, diarrhea (from all causes) is common in Mexico and may not be viewed as an illness that requires healthcare contact [15]. The reported prevalence of IBS is likely to be higher in communities with higher perceived stress, lower perceived quality of life, greater potential gain from receiving a diagnosis, or fewer barriers to health care access [4; 16; 17].

The absence of a criterion-standard case definition or standardized diagnostic criteria over time has created difficulty in defining IBS cases for epidemiologic studies. Widely used ancillary data in other disorders are limited in IBS. Relatively few patients are hospitalized for IBS or diagnosed during admission, and IBS is not a cause of death that would show on death certificates [4]. Prescription data are only recently relevant as more medications have received U.S. Food and Drug Administration (FDA) approval for IBS.

COMMON COMORBID CONDITIONS

IBS is a clinical syndrome often combined with additional comorbidities. Most cluster into functional somatic syndromes (e.g., fibromyalgia, chronic fatigue syndrome, chronic pelvic pain), other GI disorders (e.g., gastroesophageal reflux disease, dyspepsia), and psychiatric disorders (e.g., major depression, anxiety, somatization). These syndromes overlap on multiple dimensions [5; 18].

Patients with panic disorder may suffer from IBS as well; the prevalence of IBS symptom characteristics in patients with panic disorder is 25% to 44% [12]. A strong association is also found between IBS and generalized anxiety disorder, and patients with comorbid IBS and generalized anxiety disorder have greater functional impairment and depressive symptoms. Post-traumatic stress disorder (PTSD) is also prevalent, and as many as 36% of patients with IBS meet the criteria for lifetime diagnosis for PTSD. Major depressive disorder is the most frequent psychiatric comorbidity in IBS. Patients with major depressive disorder showed a 27% to 47% prevalence of IBS, although patients with major depressive disorder in remission did not differ from healthy controls in terms of IBS symptoms [12].

IBS severity and abdominal pain intensity vary directly with the degree of anxiety and depression [19]. Significantly greater levels of anxiety have been found in patients with IBS-D than in patients with IBS-C or IBS-M; patients with IBS-D also show significantly greater incidence of depression [18].

A higher percentage of patients with IBS and anxiety or depression had extra-intestinal physical symptoms than patients without anxiety (44.8% versus 16.8%, respectively) or depression (57.0% versus 21.5%, respectively) [20; 21].

Patients with IBS are much more likely to have psychiatric conditions than persons without IBS. Many patients with IBS receive anxiolytics and antidepressants, and one study found that 62% of patients had received these agents prior to being diagnosed with IBS. A greater percentage of patients with severe IBS have at least one psychiatric disorder compared with patients with mild or moderate IBS (94.4% versus 35.7% and 76.1%, respectively) [21; 22; 23].

IBS, fibromyalgia, chronic fatigue syndrome, temporomandibular joint (TMJ) disorder, and vulvodynia syndrome are characterized by distressing symptoms of pain and fatigue in the absence of clinically obvious pathology. These conditions have been termed "central sensitivity syndromes." Neuroimaging studies using evoked sensory paradigms have revealed a common sensory augmentation to both painful and nonpainful stimulation, a transformative observation for these syndromes historically considered entirely hysterical or feigned in origin. Whether amplified pain is causal to these syndromes, a predisposing factor, an endophenotype, or an epiphenomenon cannot be discerned without additional research [24].

Roughly 50% of all patients with IBS also experience fibromyalgia, chronic fatigue syndrome, chronic back pain, chronic pelvic pain, chronic headache, or TMJ dysfunction. Symptoms of these functional somatic syndromes considerably overlap with IBS and with each other, and functional somatic syndromes occur almost twice as often in patients with IBS than in the general population [25; 26]. In a survey of patients with IBS, 69% reported fatigue, 48% experienced sleep problems, and 37% complained of recurrent or chronic back pain [20; 27]. Low back pain was found to be more common in patients with IBS-C than IBS-D [21].

The symptoms of IBS are more severe in patients with somatic comorbidities than in those with IBS alone. More than 50% of patients with IBS also have depression or anxiety and, as a group experience more severe somatic symptoms than patients without these psychiatric conditions [4; 28; 29]. Many physical symptoms affect the overall well-being of patients with IBS (including psychological health) and should not be overlooked or marginalized [21].

At the time of IBS diagnosis, the likelihood of an organic lesion being found on colonoscopy in patients lacking alarm symptoms is no higher than in healthy controls, and even most patients with alarm symptoms have no organic pathology [4; 30]. In contrast to endoscopy findings at diagnosis, the subsequent risk of developing inflammatory bowel disease was found to be 9 to 16 times greater in patients diagnosed with IBS than the general population, with an average two- to three-year interval between onset of IBS and the inflammatory bowel disease diagnosis. These data implicate some overlap in pathogenesis for IBS and inflammatory bowel disease [31].

Colorectal cancer incidence is around 1% in the first year of IBS diagnosis. While initially higher than in the general population, the incidence of colorectal cancer among patients with IBS returns to population levels after one year [4; 32].

NATURAL HISTORY

Symptom Patterns

For most patients with IBS, the symptoms of IBS are intermittent and over time show considerable fluctuation in frequency and duration. In the first three months after diagnosis, patients experience an average of four distinct symptom episodes per month, with the longest episode averaging five days, and most patients experience symptoms more than 50% of the days. One year after initial diagnosis, 30% to 45% of patients report they now have pro-

longed symptom-free periods. In the second year of follow-up, some patients experience symptom resolution, while others develop new symptoms and rate of symptomatic IBS episodes remains stable. After 10 years, 50% to 70% of patients report persistent symptoms [33; 34; 35].

Long-term follow-up data from clinical IBS populations indicate that 2% to 18% of patients worsened, 30% to 50% remained unchanged, and 12% to 38% improved over time. Poor outcomes were associated with previous surgery, longer disease duration, higher somatic scores, and higher baseline levels of anxiety or depression [5; 36].

Up to 67% of patients with IBS experience functional dyspepsia. Among patients who report IBS symptom resolution, 45% subsequently develop other functional GI disorders [25; 37; 38]. Even if all GI symptoms resolve, many patients with IBS develop symptoms of other functional disorders. Patients with lower quality of life and higher levels of anxiety are most susceptible to comorbid functional disorders. Converging evidence suggests IBS is one expression of an underlying predisposition for functional disease [4; 25; 39; 40; 41].

Patients may also experience migration between predominant symptoms and IBS subtypes over time. Most commonly, IBS-C or IBS-D switches to IBS-M; switching between IBS-C and IBS-D is less common. A possible confounding factor in natural history studies of IBS is the effect of treatment, which can result in difficulty discerning symptom variation due to medical intervention versus true natural history [5; 42].

With the passage of time, overlapping symptoms and adjustments in the prevailing diagnostic subtype within a given patient are very common. In one study of 432 primary care patients with IBS-C or functional constipation followed over 12 months, roughly 33% had a change in dominant diagnosis from functional constipation to IBS-C or from IBS-C to functional constipation [43; 44]. In a cohort of female patients with IBS initially classified as constipation, diarrhea, or mixed subtypes, roughly 25% had the same subtype at 12-month follow-up, while 75% made at least one transition into another subtype [45].

Evidence of lower IBS prevalence in older age groups suggests symptom resolution over time, which is contradicted by natural history studies showing symptom chronicity. One explanation is that the diagnosis changes, rather than resolves. As discussed, patients with IBS have a high prevalence of other functional syndromes. In addition, "symptom shifting" occurs in some patients, characterized by resolution of functional bowel symptoms followed by development of extra-intestinal functional symptoms [4].

Mortality

Although patients with IBS have a significantly reduced quality of life, greater risk of depression and suicidal ideation, and higher frequency of invasive procedures and surgery, community-based studies have not associated IBS with increased mortality risk [4; 46].

DISEASE BURDEN

Like many chronic functional disorders, the overall burden of IBS can be high and medical treatments often suboptimal. Patients with IBS exhibit high rates of psychopathology, low quality of life, and increased suicidal ideation. These patients also miss more days of work, are less productive at work, and use many healthcare resources [47].

IBS significantly diminishes emotional, physical, and occupational functioning and health-related quality of life. In the United States, IBS accounts for 3.1 million ambulatory care visits and 5.9 million prescriptions annually, with total direct and indirect annual expenditures exceeding $20 billion [5; 48].

The diagnosis and management of IBS are predominantly issues for ambulatory medicine. In 2010, IBS accounted for just 0.03% of U.S. hospital discharges, with a mean inpatient stay of 3.7 days costing a mean $21,153 [49].

The impact of IBS subtypes on quality of life was evaluated in 542 patients with IBS in the United States using the IBS Quality of Life (IBS-QOL) questionnaire (overall and subscale scores range 0–100, with higher scores suggesting better quality of life). Overall IBS-QOL scores of patients with IBS-D (61.6) and IBS-M (63.0) were lower than those of patients with IBS-C (74.5). Patients with IBS-D scored lower than those with IBS-C on food avoidance (45.0 vs. 61.1) and interference with activity (59.6 vs. 82.3). Compared with patients with IBS-C, patients with IBS-M had greater interference in activities (61.6 vs. 82.3) and impact on relationships (73.3 vs. 84.7). Patients with IBS-M scored lower than IBS-C on food avoidance (47.2 vs. 61.1) and concern over negative social reaction (66.1 vs. 80.0) [50].

Patients with IBS-D or IBS-M are more likely to avoid culprit foods perceived to be symptom triggers than patients with IBS-C. IBS had a significantly greater negative impact on relationships in patients with IBS-M than in those with IBS-C, and more than 50% reported workplace embarrassment. Interpersonal problems were more pronounced in patients with IBS-D. This study indicates that clinicians should pay special attention to food avoidance and negative effects on relationships, daily activities, and social reaction in patients with IBS-D and IBS-M, as these domains influence significantly the quality of life [50].

Bloating is perhaps the most bothersome IBS symptom to patients. Bloating often leads to seeking medical care and adversely affects energy level, food intake, and physical functioning [51]. A large population-based study in Japan found abdominal bloating to be the most bothersome symptom in patients with IBS-C. The levels of anxiety and distress in daily life were associated with severity of abdominal pain, discomfort, and bloating, and abdominal bloating was more likely to occur after a meal, at work/school, and during times of stress [52].

The social burden of IBS, in particular IBS-C, impacts workforce efficiency and productivity. A study using measures of daily work activity and past-week work productivity found the average rate of past-week absenteeism among American patients with IBS-C was 10.6% [221]. In addition, 37.4% reported presenteeism, 39.3% overall work productivity loss, and 45.7% daily activity impairment due to general health problems over the past week. The economic impact of lost productivity was estimated to be $155 per employed patient/week, suggesting IBS-C-related impairment is a significant burden for patients and employers [53].

Perceived stigma is an important consideration in patients with IBS. Patients with symptoms of IBS or other functional disorders present for medical care with painful, embarrassing, and life-limiting symptoms that lack objective confirmation on routine diagnostic exam and laboratory workup. Moreover, the common inclusion of IBS and fibromyalgia in psychiatric diagnostic classification systems as somatoform disorders (e.g., psychological distress manifesting as physical symptoms) adds to the consternation. Lacking a consistent and valid illness concept or suitable term for the disorder, some caregivers may be tempted to label the patient with dismissive terms like "difficult patient," "frequent attender," or "heart-sink patient." This type of labeling may result in patient reluctance to seek medical care [54].

ETIOLOGY, PATHOGENESIS, AND PATHOPHYSIOLOGY

GI syndromes/symptoms may be classified into three general diagnostic categories: organic, motility, or functional disorders [2; 15]. Organic (or structural) disorders are characterized by macro- or micro-level pathology of organs or structures and include esophagitis and inflammatory bowel disease. Motility disorders are characterized by pathology of organ (motility) function. Examples of motility disorders are gastroparesis and intestinal pseudo-obstruction.

Functional GI disorders are idiopathic disorders of gut-brain interaction and, unlike organic disease and motility disorders, diagnosis involves identification of symptom clusters. These disorders may be further categorized as functional bowel, functional esophageal, IBS, noncardiac chest pain, functional gastroduodenal, and other disorders.

IBS is a functional bowel disorder, as are functional constipation, functional diarrhea, and functional abdominal bloating/distension. A more precise term is "disorders of gut-brain interaction," as functional GI disorders develop from complex, bidirectional interactions of biopsychosocial factors. These environmental, psychological, and biologic factors interact to drive the genesis, clinical expression, and chronicity of functional GI disorders (***Table 1***) [2; 15].

Psychosocial factors such as early life events, trauma, social learning, and/or psychiatric and psychological disorders influence the brain and gut, which interact bidirectionally via the autonomic nervous system and hypothalamic-pituitary-adrenal (HPA) axis through brain-gut mediation. The integrated effects of altered physiology and psychosocial status shape the illness experience and clinical outcome, which in turn influences the severity of the disorder [55].

IBS pathophysiology is complex and multifactorial. Genetic, environmental, and psychosocial factors increase the risk of developing IBS. Factors that trigger IBS onset or exacerbation include gastroenteritis, food intolerances, chronic stress, and surgery. Pathophysiologic mechanisms vary but commonly include altered colonic motility, visceral hyperalgesia, increased intestinal permeability, immune activation, altered microbiota, and disturbances in central nervous system (CNS) function [3].

FACTORS AFFECTING THE DEVELOPMENT, EXPRESSION, AND CHRONICITY OF FUNCTIONAL GI DISORDERS

Genetic and environmental factors
Genetic polymorphism Early life experiences Parental beliefs and behaviors Social learning, support, stress Trauma Infection
Psychological factors
Psychopathology (anxiety, depression) Cognitive-affective processes: • Health anxiety and somatization • GI-specific anxiety • Attentional bias/symptom hypervigilance • Catastrophizing
CNS structure and function
Structural brain abnormalities Functional network connectivity Emotional and cognitive modulation of visceral afferent signals Fear conditioning
Gut physiology
Gut permeability Motility Sensation Altered bacterial flora Inflammation and immune dysfunction

Source: [2; 15] *Table 1*

CONTRIBUTING FACTORS

Familial and Environmental Factors

Childhood Social Learning

Childhood functional GI disorders aggregate in families. Research into genetic factors is ongoing, but what children learn from parents is considered a greater contributor to the risk for developing functional GI disorders. One important contributor is the learning principle of positive reinforcement or reward. Children whose mothers reinforce illness behavior experience more severe stomachaches and more school absences than other children. In

children with functional abdominal pain, cognitive-behavioral therapy (CBT) designed to improve parent and child coping strategies and beliefs about (and responses to) the child's complaints is more effective for relieving pain and reducing symptoms than an educational intervention. This effect is mediated by changes in parents' cognitions about their child's pain [39; 55; 56].

A strong association is found between parental psychological status (e.g., anxiety, depression, somatization) and children's abdominal symptoms [57]. This association may occur through modeling, whereby children observe and learn to display the behaviors they observe—in this context, heightened attention to or catastrophizing about somatic sensations. This effect of parental traits on children's symptoms can also occur through reinforcement. Parents with certain traits or beliefs (e.g., excessive worry about pain) might pay more attention to and reward somatic complaints. Parental catastrophizing about their own pain reinforces these types of responses to abdominal pain in their children, which encourages illness behavior and predicts child functional disability [55; 58; 59].

Childhood and Adult Stressors

Early life trauma is associated with increased risk for IBS and other functional GI disorders, major psychiatric disorders, ischemic heart disease, diabetes, asthma, and other medical disorders in adulthood [60]. In general, patients with IBS report a high prevalence of adverse life events, including childhood physical punishment, emotional abuse, and sexual abuse. This psychosocial history is related to greater functional GI disorder severity and higher rates of psychological distress and impaired daily functioning. These effects increase health care seeking and explain the higher prevalence of abuse histories among patients with IBS seen in specialty clinics than in primary care; those with mild IBS symptoms and psychosocial histories may not seek medical care. A past history of childhood abuse is also common (approaching 50%) in patients with chronic functional somatic syndromes such as chronic pelvic pain, headaches, and fibromyalgia [61; 62; 63].

Functional GI disorder onset frequently coincides with experiencing a highly threatening event, such as the breakup of an intimate relationship. Stressful life events are associated with symptom exacerbation and frequent health care-seeking in adults with IBS. Chronic life stress is the greatest predictor of IBS symptom severity one to two years after diagnosis and negatively affects functional GI disorder treatment outcomes. Presence of a single stressor within 6 months of initiating IBS treatment predicts poor outcomes and higher symptom intensity at 16-month follow-up [55; 64].

Social Support

Quality of social support is related to many aspects of IBS. Patients have reported that finding social support helps them overcome IBS. Perceived social support adequacy is linked to IBS symptom severity, possibly through reducing stress levels. Negative social relationships with frequent conflict and adverse interactions consistently show a greater impact on poor outcomes than the absence of social support. A supportive patient-practitioner relationship improves symptoms and quality of life in patients with IBS, showing the clinically valuable role of social support [55; 65; 66].

Psychological Factors and Psychiatric Disorders

Psychological distress is an important risk factor for developing functional GI disorders. The presence of psychological comorbidity may perpetuate or exacerbate symptoms and negatively affects the clinician-patient relationship and treatment outcomes. Comorbid anxiety or depression strongly predicts postinfectious IBS and functional dyspepsia and is also associated with severity of symptoms and quality of life impairment. The absence of co-occurring psychiatric comorbidity does not exclude contribution to functional GI disorder from dysfunctional cognitive and affective processes.

Mood Disorders

The overlap between major depressive disorder and functional GI disorder is about 30% in primary care and slightly higher in specialist care. Depression can influence the number of functional GI symptoms and diagnoses. Suicidal ideation is present in 15% to 38% of patients with IBS and is linked to hopelessness surrounding symptom severity, interference with life, and an unsatisfactory response to treatment. Comorbid major depressive disorder is linked to poor outcomes, including high health care utilization and cost, functional impairment, poor quality of life, and poor treatment engagement and outcomes [67; 68; 69].

Anxiety Disorders

Anxiety disorders are the most common psychiatric comorbidity in patients with functional GI disorders, with an estimated prevalence of 30% to 50%. Anxiety can initiate or perpetuate functional GI disorder symptoms by amplifying autonomic arousal (in response to stress) or interfering with GI sensitivity and motor function. Common pathways might exist between vulnerability to anxiety disorders and functional GI disorders, especially through anxiety sensitivity, bodily vigilance, and discomfort intolerance [67; 70].

Somatization, Somatic Symptom Disorder, and Functional Somatic Syndromes

In the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5), somatic symptom disorder replaced the abandoned term "somatization," which described patients who responded to psychosocial stress by experiencing, communicating, and seeking medical help for physical symptoms unconfirmed by pathologic findings. The number of symptom complaints was emphasized [55; 71].

In the DSM-5, somatic symptoms may or may not have a specified medical diagnosis but are distressing, disabling, and associated with excessive and disproportionate thoughts, feelings, or behaviors persisting longer than six months. This designation shifts the experience of medically unexplained symptoms from subconscious manifestations of psychological distress to the abnormal cognitive-affective processes surrounding the symptoms [55; 72; 73].

Gastrointestinal somatization is associated with processes such as gastric sensitivity and emptying, symptom severity, and impaired quality of life. It is linked to higher health care use and predicts poor treatment response and discontinuing medication from side effects. Somatization is used extensively in the medical literature to account for syndromes, often with pain the prominent symptom, that lack apparent physiologic cause following standard diagnostic workups. In assessing possibility of somatization, it is clinically useful to consider the severity of the multiple somatic symptoms [73; 74; 75].

Somatization may explain the extra-intestinal symptoms experienced by patients with IBS and the common occurrence of other functional somatic syndromes among patients with IBS. The overlap is extensive; 67% of patients with functional GI disorders also have a positive history for conditions such as interstitial cystitis, chronic pelvic pain, headaches, fibromyalgia, or other functional somatic syndromes, independent of psychiatric comorbidity [55; 76; 77].

Cognitive-Affective Processes

The psychological constructs of health anxiety, GI symptom-specific anxiety, attentional bias/symptom hypervigilance, and catastrophizing are linked to functional GI disorders independent of psychiatric comorbidity (***Table 2***). These are important treatment targets for CBT [55].

GI symptom-specific anxiety is an important perpetuating factor that describes threatening interpretation and out-of-proportion behavioral response to GI sensations. This anxiety is characterized by worry and hypervigilance around GI sensations common to normal bodily functions (e.g., hunger, satiety, gas) as well as to symptoms of an existing GI condition (e.g., abdominal pain, diarrhea, urgency). Worry and hypervigilance generalize into fear about when sensations/symptoms will occur and about the social contexts where this could happen. Avoidance or behaviors disproportional to symptoms follows [55; 78].

COGNITIVE-AFFECTIVE PROCESSES INFLUENCING THE SYMPTOM EXPERIENCE IN FUNCTIONAL GI DISORDERS (FGIDs)				
Term	**Definition**	**Association with FGID**	**Outcomes**	**Management**
Illness anxiety	Global tendency to worry about current and future bodily symptoms, formerly referred to as hypochondriasis	Low insight Extensive research into what is wrong Not easily reassured Lack of acceptance Rick factor for the development of FGID	Chronicity Social dysfunction Occupational difficulties High health costs Negative physician-patient relationship Poor treatment response	Responsive to CBT
Symptom-specific anxiety	Worry/hypervigilance around the likelihood/ presence of specific symptoms and the contexts in which they occur	Belief that normal gut sensations are harmful or will lead to negative consequences Promotes GI symptoms	Drives health care use Negatively impacts treatment response	Aerophagia improved with distraction May be differentially responsive to interoceptive exposure-based therapy
Hypervigilance/ attentional bias	Altered attention toward, and increased engagement with, symptoms and reminder of symptoms	Patients with IBS: Higher recall of pain words and GI words compared with healthy controls Patients with NCCP: Hypervigilance toward cardiopulmonary sensations	Dismiss signs of improvement Ignore information suggesting FGID is not serious	Responsive to CBT
Catastrophizing	Individual magnifies the seriousness of symptoms and consequences while simultaneously viewing him/herself as helpless	Symptom amplification Increased pain Inhibits pain inhibition Negatively affects interpersonal relationships Leads to increased worry, suffering, disability	High symptom reporting Reduced quality of life Can impact patient self-report Burdens provider	Improves with CBT Mediates outcome

CBT = cognitive-behavioral therapy, NCCP = noncardiac chest pain.

Source: Reprinted from Van Oudenhove L, Levy RL, Crowell MD, et al. Biopsychosocial aspects of functional GI disorders: how central and environmental processes contribute to the development and expression of functional GI disorders. Gastroenterology. 2016;150(6):1355-1367, with permission from Elsevier. *Table 2*

As an example, a person with IBS who has not eaten all day becomes aware her stomach is rumbling. This is interpreted to mean that the need to defecate may be imminent, triggering anxiety about whether and how this can be managed, as she is in public with friends. The anxiety increases when no restroom is visible, and the person leaves her friends for fear they would not understand [55].

Other Factors

Genetic Predisposition

Variations in the gene that encodes serotonin reuptake transport system have been found in patients with IBS. It is believed that polymorphism of the 5-HT2A receptor gene may be associated with the development of IBS [79].

Acute Infectious Gastroenteritis

The prevalence of IBS is increased six- to seven-fold in persons who have experienced a prior infectious gastroenteritis or enterocolitis, and postinfectious IBS accounts for 5% to 25% of all cases of IBS [80]. IBS develops in 3% to 30% of patients following acute gastroenteritis, illustrating an acute pathogen and host interaction that predisposes to development of chronic IBS [5; 81]. Factors with the greatest risk for postinfectious IBS are elongating toxin and longer duration of the initial illness [82; 83]. Other predisposing factors include:

- Female sex
- Younger age
- Toxicity/severity of infecting strain
- Cigarette smoking
- Mucosal inflammation
- Immune function
- Microbiome
- Concurrent depression or anxiety
- GI infection severity
- Antibiotic treatment

Psychopathology increases the risk of developing postinfectious IBS by enhancing susceptibility to infectious gastroenteritis [5; 84]. Mucosal inflammation and abnormal gut-host microbial interactions also promote postinfectious IBS. Mucosal immune activation and immune cell proliferation may amplify peripheral sensory signaling to result in visceral hypersensitivity, a primary IBS pain mechanism [5; 84].

Patients with postinfectious IBS are important to identify because roughly 50% will experience spontaneous remission within six to eight years of the initial infection. This disease course differs from the chronic relapsing nature of typical IBS [5; 85].

Acute gastroenteritis is now known to cause marked disruptions in the gut microbiota by pathogen overgrowth and substantial reduction in the diversity of normal flora. In the past, gut equilibrium was assumed to normalize after the infection cleared. However, research indicates individuals recovering from *Campylobacter jejuni* enteritis (a common cause of food poisoning) are as likely to show continued alteration in microflora (with potential progression to IBS-D) as they are full recovery of gut equilibrium [86; 87].

Alterations in the Intestinal Microbiome

Gut dysbiosis is defined as an imbalanced or maladapted, but stable, gut ecosystem that has potential for reducing homeostasis and increasing the risk of disease pathogenesis [88]. Gut dysbiosis may influence the natural history of psychiatric disorders, cognitive disorders, and chronic visceral pain (due to brain-gut mediation). The intestinal flora of patients with IBS differs from healthy persons, and intestinal flora profiles also differ among IBS subtypes [89]. Deficiency in *Bifidobacterium* has been associated with greater abdominal pain and bloating. As such, treatment with probiotics has shown some promise in alleviating symptoms in IBS. In one study, probiotic administration was found to alter central processing of emotional stimuli and resting brain connectivity in sensory and affective brain circuits. The hypothesis of a microbiome gut-brain axis is emerging, and there is a possibility that gut microbiota will represent a therapeutic target in the treatment of IBS [55; 90; 91].

Bile Acids and Bowel Dysfunction

Secretory diarrhea arises from colonic perfusion of bile acids caused by inadequate ileal reabsorption (less than 95%). Excess bile acids entering the colon increase gut permeability, activate adenylate cyclase, stimulate colonic secretion, and increase stool water and colonic motility. Decreased circulating fibroblast growth factor 19 (FGF19) leads to excessive bile acid production and can be primary or secondary to ileal resection or ileitis. Around 10% of patients with IBS-D have severe bile acids malabsorption—defined as less than 5% retention at seven days. In the United Kingdom, bile acid diarrhea accounts for nearly 25% of patients with IBS referred to specialist care for diarrhea [87; 92].

The presence of bile salt overproduction is identified by measuring the seven-day retention of a synthetic radiolabeled bile acid, selenium-75 homocholic acid taurine (SeHCAT). However, access to SeHCAT is limited; another approach measures fasting FGF19 using an enzyme-linked immunosorbent assay (ELISA). FGF19 <145 pg/mL predicts reduced SeHCAT retention [87].

The cause of low FGF19 levels is not fully known, but bile acid malabsorption can begin acutely after an ileitis episode, common with *Salmonella* spp. or *C. jejuni* gastroenteritis. Sudden onset and high-volume nocturnal diarrhea are characteristic features [87].

The prevalence and role of ileal malabsorption of bile acids in diarrhea-like symptoms has historically been underestimated in IBS-D. Identification can lead to specific treatment with bile acid sequestrants [15; 93].

Diet

Many patients report that certain foods trigger IBS symptoms. The contribution of true food allergies is small, but food intolerances are common in patients with IBS. Gluten (present in wheat products) is increasingly recognized as an important symptom trigger in patients with IBS and inducer of IBS-like symptoms in persons without IBS diagnosis. Non-celiac gluten sensitivity is an emerging syndrome provoked by gluten ingestion in patients in whom celiac disease and wheat allergy are ruled out. Other triggers of non-celiac gluten sensitivity pathogenesis include wheat proteins (i.e., amylase and trypsin inhibitors) and FODMAPs (fermentable oligo-, di-, monosaccharides, and polyols) [94; 95]. Emerging evidence supports gluten-free and low-FODMAPs diets for patients with IBS. FODMAPs are poorly absorbed carbohydrates that can induce osmotic effects, result in increased fermentation in the small bowel or colon, and trigger symptom exacerbation in patients with IBS with abnormal gut function or sensitivity [5; 94].

Dietary constituents also influence the impact of intraluminal factors on gut function. Among these are microflora alterations in short-chain fatty acids; the effects of enteroendocrine cell products (i.e., granins) on nervous, endocrine, and immune cells; and the ratio of secondary to primary bile acids that impact gut transit rates [15; 96].

A six-week placebo-controlled, double-blind trial in patients with IBS with gluten sensitivity histories found poorly controlled IBS symptoms in 68% randomized to diets with gluten, compared with 40% receiving a gluten-free diet. In patients receiving a gluten-free diet, double-blinded gluten re-challenge worsened pain, bloating, stool consistency, and fatigue [97]. A study of patients with IBS-D reported that gluten administration led to altered gut permeability and increased stool frequency and immune activation [98].

While these data suggest that symptom exacerbation after ingesting wheat is primarily caused by gluten, wheat also contains fructans and other proteins that may trigger symptoms in patients with IBS [5]. A clinical trial of 920 patients with IBS found that 33% of subjects experienced worsened symptoms of increased abdominal pain and distension after receiving wheat (not limited to gluten), but not after placebo [99].

BRAIN-GUT AXIS AND PROCESSING

Bidirectional interactions involving components of the (peripheral) GI system (microbiome, altered mucosal inflammation, visceral hypersensitivity) and the CNS (emotional arousal, sensorimotor function, salience and executive function, central autonomic function) contribute to the development of IBS. Neurophysiologic mechanisms in the brain-gut axis link psychological processes, psychiatric comorbidity, and IBS symptoms [2; 100].

Homeostatic information about visceral physiologic status is continuously signaled to the brain through afferent neural and humoral "gut-brain" pathways. Under normal conditions, humans have no conscious perception of most gut-brain signals. Visceral pain results from the perception of strong gut-brain signaling, triggered by noxious stimuli to warn of potential threat to homeostasis that requires a response [55; 100].

Visceral afferent signals are relayed to the brain, then processed, modulated, and integrated by means of the afferent network, emotional arousal, and cortical modulatory neurocircuits [55]. Emotional arousal and cortical modulation circuits project "top-down" to brainstem areas, which send descending projection neurons to dorsal horns of the spinal cord, where pain transmission is modulated. This circuitry is termed the descending pain modulation system (DPMS) [55].

ALTERED PAIN PERCEPTION IN PATIENTS WITH IBS

The hallmark symptom of IBS in the Rome IV criteria is chronic visceral pain and/or discomfort, and patient perception of visceral pain in IBS is disproportionate to the intensity of visceral afferent inputs, which is the result of complex psychobiologic processes [55].

Visceral hypersensitivity (also referred to as sensitization) describes lowered thresholds for visceral pain and occurs in the majority of patients with IBS. In these patients, lower pain thresholds are reflected by an exaggerated pain response to normally modest GI discomfort and/or painful response to stimuli that are not normally pain- or discomfort-inducing (e.g., normal bowel function). Visceral sensitivity is amplified in patients with IBS [15].

Psychological processes and psychosocial factors substantially influence visceral hypersensitivity. In patients with IBS, hypervigilance (defined as a heightened psychological tendency to focus on and report pain) is considered a greater contributor to lowered pain thresholds than actual increased neurosensory sensitivity. Anxiety and depression levels are directly related to pain severity in patients with IBS [101; 102; 103; 104].

As discussed, extra-intestinal chronic pain conditions are highly prevalent in IBS, and widespread hypersensitivity and extra-intestinal pain syndromes suggest CNS involvement and central sensitization. Descending neural modulatory circuits from the brain can inhibit or facilitate ascending nociceptive transmission, influenced by cognitive processes and mood. Changes in DPMS function are thought to influence pain perception [105]. Dysregulated cortical modulation of descending pain regulatory pathways can amplify sensitivity to noxious and innocuous stimuli [106].

Neural pathways play a major role in modulating visceral pain experience and other IBS symptoms. Spinothalamic tracts localize and differentiate visceral stimuli, while spinoreticular pathways influence the reflexive, affective, and motivational aspects of pain sensation [81]. Pain modulatory system dysfunction promotes visceral hypersensitivity, and studies of IBS have shown abnormalities in pain signal processing and modulation that include functional and structural abnormalities in sensory, emotional arousal, and prefrontal cortical modulatory regions [55; 106].

Altered Brain Network Function

In IBS, colorectal distension activates brain stress response areas but deactivates brain areas that modulate stress response [80; 107; 108]. This pattern reflects up-regulated connectivity in emotional arousal circuitry and helps explain the increased sympathetic arousal, anxiety, and vigilance often

observed in patients with IBS, and the association between IBS symptoms and functional alteration in multiple brain networks [55].

When anticipating experimentally induced visceral pain, anticipatory response in the locus coeruleus predicts subjective perception and brain response to the actual painful stimulus. Sensory filtering is degraded by anxiety-related dysfunction of the descending pain modulation system [107; 109].

Altered Brain Structure

Alterations in brain structure have been demonstrated in patients with IBS. The role of structural brain changes in IBS and other functional pain disorders is not clear, because these changes may represent pre-existing vulnerability factors or consequences of long-term exposure to the pain [106].

Female patients with IBS have shown increased cortical thickness in the somatosensory cortex and decreased cortical thickness in pain processing regions, including the insula and anterior cingulate cortex. IBS symptom severity is negatively correlated with cingulate thickness, suggesting a role for loss of neural density in symptom generation [106; 110; 111].

Patients with IBS have also shown decreased gray matter volumes in widespread regions, with early life trauma contributing to these decreases [106]. Decreased gray matter density in prefrontal and posterior parietal cortex areas is consistent with the close relationship between IBS and mood disorders. Pain catastrophizing negatively correlates with the degree of cortical thickness in the prefrontal cortex [112; 113; 114].

Structural abnormalities of brain white matter tracts have been found in multiple areas of the brain in patients with IBS. These white matter changes are associated with symptom severity, trait anxiety, and catastrophizing [115; 116; 117].

CLINICAL PRESENTATION AND DIAGNOSTIC WORKUP

CLINICAL PRESENTATION

Abdominal Pain

Descriptions of pain associated with IBS often change, but the pain is typically described as cramping discomfort that is diffuse or variable in location, without radiation. The most common site of pain is the lower abdomen, specifically the left lower quadrant. Many patients experience periodic exacerbations that vary in intensity from mild to severe; others describe acute episodes of sharp pain, often superimposed on a more constant dull ache. Meals may precipitate or aggravate the pain. Some patients report that pain is worsened by defecation, others that the pain is relieved by defecation. On occasion, the combination of enhanced colonic peristalsis and trapped gas in the splenic flexure may produce severe left upper quadrant abdominal pain or referred pain to the chest that mimics that of cardiac ischemia. Termed splenic flexure syndrome, balloon inflation in the splenic flexure will provoke this pain and should be considered in selected patients in order to differentiate it from more serious causes of chest or left upper quadrant abdominal pain [118].

Altered Bowel Habits

Altered bowel habits may be described as diarrhea, constipation, or alternating diarrhea and constipation. Some patients have periods of relatively normal bowel habits alternating with episodic periods of either diarrhea or constipation. Patients with predominant constipation often report painful and infrequent defecation, non-response to laxatives, often associated with passage of hard, pellet-like or narrow stools. Diarrhea is usually described as small volumes of loose stool preceded by urgency or frequent defecation. Postprandial urgency is common. [118]. Stools may also be white or clear (mucosa).

Abdominal Distention

Patients with IBS frequently report increased amounts of bloating and intestinal gas, but confirmation by quantitative measurements is elusive. People with IBS can experience expanding, and measurable, abdominal circumference throughout the day. Intolerance of otherwise normal amounts of abdominal distention is common [118].

Other Common Symptoms and Complaints

Dyspepsia, heartburn, nausea, vomiting, sexual dysfunction (including dyspareunia and poor libido), and urinary frequency and urgency frequently occur in patients presenting with IBS complaints. Fibromyalgia commonly co-occurs. Careful questioning can reveal stressor-related symptoms; if disclosed, ask further about avoidance of stressors [118].

Perimenstrual Symptom Exacerbation

Many women of reproductive age experience cyclical changes in GI symptoms (including alteration in bowel habits) during their menstrual cycle. Female patients with IBS often experience worsened GI symptoms of abdominal pain, bloating, or diarrhea during menses, possibly due to elevated prostaglandin levels during menses that enhance perception of viscera-somatic stimuli and increases nausea, abdominal distension, and pain [119].

Fatigue

Despite receiving little attention in the medical literature, fatigue is a frequent symptom in patients with IBS and is associated with poor quality of life. A study of 160 patients with IBS found a multidimensional and negative impact from fatigue on daily life [120]. Fatigue may interfere with patients' ability to perform physical activities, work, domestic work, and interact socially. Poor stamina is the most prominent feature, and strategies to limit the bodily consequences of tiredness are common. Severe fatigue is associated with more severe IBS symptoms, anxiety, and depression. Fatigue is a distressing symptom in a sizeable proportion of patients with IBS and should be assessed and, if confirmed, targeted for intervention [120].

CONCEPTUAL AND DIAGNOSTIC ADVANCES

Over time, the definitions of IBS and functional GI disorders have been shaped by societal perspectives of illness and disease, available scientific evidence, and clinician training and bias. Even today, some consider functional GI disorders to be "less legitimate" than pathologically based disorders, and patients with functional GI disorders may be stigmatized for having functional symptoms. This is a carry-over from the influence of dualistic principles that dichotomized organic disorders from functional disorders, which were often considered psychiatric or undefined. However, the definition has changed from the absence of organic disease, to a stress-related or psychiatric disorder, a motility disorder, a disorder of GI functioning, and finally to a disorder of gut-brain interaction [2].

The Rome Foundation was founded in the 1980s to promote global recognition of functional GI disorders, advance scientific understanding of functional GI disorder pathophysiology, optimize clinical management for patients with functional GI disorders, and develop educational resources to achieve these goals. The Foundation is comprised of scientists and clinicians from around the world with expertise in diverse areas relevant to functional GI disorders [121].

The Rome III criteria incorporated scientific data on IBS diagnosis and treatment. Rome III defined IBS as recurrent abdominal pain or discomfort three or more days per month in the preceding three months, with two or more of the following: symptom improvement with defecation, onset of symptoms coupled with altered stool frequency, or onset coupled with altered stool form [122; 123].

Over the past decade, the need to revise Rome III became increasingly apparent. Knowledge of IBS pathophysiology continued evolving, and many clinicians found Rome III criteria unhelpful and lacking in real-world clinical applicability. For example, Rome III did not recommend basic laboratory testing and ignored the fact that, for many patients, abdominal pain worsened rather than improved with defecation. Some Rome III criteria were seen as vague or incorrect [122].

In 2016, the Rome IV guidelines were published to address these criticisms and improve guidance to healthcare providers based on latest scientific and clinical evidence. Important changes in Rome IV IBS diagnostic criteria include [2; 3]:

- The term "abdominal discomfort" was removed because it was determined to be imprecise and difficult to translate.
- The required frequency and presence of abdominal pain was increased to reflect research that identified pain as a cardinal symptom of IBS.
- Rome IV recognizes that IBS is often associated with irregular bowel habits of constipation, diarrhea, a mix or alternation of each, and that common symptoms include bloating and distension.
- As IBS is a chronic condition, Rome IV requires symptom persistence for six or more months for diagnosis.
- Rome IV now acknowledges the role of diagnostic tests to exclude other common conditions with similar symptoms to IBS, such as celiac disease, lactose intolerance, and inflammatory bowel disease.
- Replacing the term "functional" was found impractical due to its pervasive use in healthcare nosology, so this term was limited to the extent possible.

By clarifying language, updating the definition, and including the option of laboratory testing, the new criteria are intended to make IBS easier to diagnose. The emphasis on abdominal pain validates clinician reports of this symptom as the essential element of IBS. Rome IV should also help differentiate IBS from intermittent abdominal spasms or cramps and chronic constipation or diarrhea [3; 122]. The revised Rome IV IBS criteria are part of a larger project by the Rome Foundation to overhaul and update scientific data, educational information, and clinical guidance to optimize the diagnosis and treatment of functional GI disorders.

Functional bowel disorders, a functional GI disorder subgroup, describe a spectrum of chronic GI disorders characterized by predominant signs or symptoms of abdominal pain, bloating, distention, and/or bowel habit abnormalities (i.e., constipation, diarrhea, or mixed constipation and diarrhea) [3]. These disorders are distinguished from other GI disorders based on chronicity (more than six months of symptoms at the time of presentation), current activity (symptoms present within the last three months), frequency (symptoms present, on average, one or more days per week), and absence of obvious anatomic or physiologic abnormalities identified by routine diagnostic workup. Functional bowel disorders include IBS, functional constipation, functional diarrhea, functional abdominal bloating/distention, unspecified functional bowel disorder, and opioid-induced constipation, a new entry that differs from other functional bowel disorders by etiology but resembles functional constipation in clinical presentation [3]. In a large multi-national study, the authors found that more than 40% of persons worldwide have functional gastrointestinal disorders [213].

Importantly, these disorders significantly overlap and should be viewed as a continuum instead of discrete diagnostic entities. Given the extent of overlap, differentiation of functional bowel disorders may not always be possible [3].

Importance of a Formal IBS Diagnosis

There are data to suggest that among persons with IBS-D symptoms, a formal diagnosis may have important implications for quality of care [9]. Patients with a formal diagnosis of IBS are more likely to have a sustained clinician-patient relationship that facilitates dialog, promotes patient education, and provides access to evidence-based therapies. As a group, these patients are better informed regarding IBS pathophysiology and more attuned to the role of aggravating factors, such as diet, stress, and the state of the intestinal microbiota.

DIAGNOSTIC CRITERIA AND MEASUREMENT SCALES

As noted, IBS is a functional bowel disorder with recurrent abdominal pain associated with defecation or a change in bowel habits. Disordered bowel habits and symptoms of abdominal bloating/distention are typically present. The formal diagnosis requires evidence of chronicity (symptom onset and duration of at least six months) and active symptoms present during the previous three months [3].

EVIDENCE-BASED PRACTICE RECOMMENDATION

The National Collaborating Centre for Nursing and Supportive Care recommends that healthcare professionals should consider assessment for IBS if the person reports having had any of the following symptoms for at least six months: abdominal pain or discomfort, bloating, and/or change in bowel habit.

(https://www.nice.org.uk/guidance/cg61. Last accessed November 18, 2022.)

Level of Evidence: Consensus Statement/Expert Opinion

For all IBS subtypes, the key requirement is that symptoms must not have an organic, metabolic, or drug-induced origin. A symptom-focused patient history and careful physical examination are mandatory to rule out intestinal or extra-intestinal diseases, symptom-inducing medications, and alarm symptoms that prompt further diagnostic exploration [44].

The Rome IV IBS diagnostic criteria are [3]:

- Recurrent abdominal pain occurring, on average, one or more days per week
- The abdominal pain is associated with two or more of the following criteria:
  - Related to defecation
  - Associated with a change in frequency of stool
  - Associated with a change in form (appearance) of stool

Diagnosis is made with criteria fulfilled the last three months and symptom duration at least six months.

Bristol Stool Form Scale

The Bristol Stool Form Scale (BSFS) illustrates and describes the appearance of seven different stool types that correspond to intestinal transit time ranging from severe constipation (Types 1 and 2) to diarrhea (Type 7). Patients can use the BSFS to record frequency and subtype of their stools [124]:

- Type 1: Separate hard lumps, like nuts (hard to pass)
- Type 2: Sausage-shaped but lumpy
- Type 3: Like a sausage with cracks in the surface
- Type 4: Like a sausage or snake, smooth and soft
- Type 5: Soft blobs with clear-cut edges
- Type 6: Fluffy pieces with ragged edges, a mushy stool
- Type 7: Entirely liquid, no solid pieces

Diagnostic Criteria for IBS Subtypes

IBS is subtyped by predominant bowel habit change, but only after all medications to treat bowel habit abnormalities are discontinued. The BSFS can be used to categorize IBS into subtypes based on stool characteristics (***Table 3***). Predominant bowel habits are based on stool form on days with at least one abnormal bowel movement [3; 44].

Diagnostic Criteria for Related Functional Bowel Disorders

Functional bowel disorders are diagnosed when criteria are fulfilled for the last three months, with symptom onset more than six months before diagnosis [3].

Functional Constipation

In order for a diagnosis of functional constipation to be made, two or more of the following must be present [3]:

- Straining during >25% of defecations
- Lumpy or hard stools (BSFS 1 or 2) in >25% of defecations
- Sensation of incomplete evacuation in >25% of defecations

DIAGNOSTIC CRITERIA FOR IBS SUBTYPES		
Subtype	**BSFS Criteria**	**Alternative**
IBS with predominant constipation (IBS-C)	>25% of bowel movements with BSFS types 1 or 2 AND <25% of bowel movements with BSFS types 6 or 7	Patient reports that abnormal bowel movements are usually constipation (BSFS type 1 or 2).
IBS with predominant diarrhea (IBS-D)	>25% of bowel movements with BSFS types 6 or 7 AND <25% of bowel movements with BSFS types 1 or 2	Patient reports that abnormal bowel movements are usually diarrhea (BSFS type 6 or 7).
Mixed-type IBS (IBS-M), in which constipation and diarrhea alternate	>25% of bowel movements with BSFS types 1 or 2 AND >25% of bowel movements with BSFS types 6 or 7	Patient reports that abnormal bowel movements are usually both constipation and diarrhea.
IBS unclassified (IBS-U)	—	Patients who meet diagnostic criteria for IBS but whose bowel habits cannot be accurately categorized into one of the other three groups.
BSFS = Bristol Stool Form Scale.		
Source: [3; 44]		*Table 3*

- Sensation of anorectal obstruction/blockage in >25% of defecations
- Manual maneuvers to facilitate >25% of defecations (e.g., digital evacuation, support of the pelvic floor)
- Fewer than three spontaneous bowel movements per week

In patients with functional constipation, loose stools are rarely present without laxative use. Although symptoms may be similar, these patients do not meet the full criteria for IBS-C.

Functional Diarrhea

Functional diarrhea is characterized by loose or watery stools (>25% of stools) without predominant abdominal pain or bothersome bloating. These patients do not meet the criteria for IBS-D.

Functional Abdominal Bloating/Distension

Functional abdominal bloating (FAB) or distention (FAD) represent two different sets of signs and symptoms but are combined by Rome IV into the diagnostic entity of FAB/FAD. In patients with FAB/FAD, mild abdominal pain related to bloating and/or minor bowel movement abnormalities may be present. Symptoms of recurrent abdominal fullness, pressure, a sensation of trapped gas, and/or measurable increase in abdominal girth must be present. Abdominal bloating and/or distention predominates over other symptoms, occurring, on average, at least one day per week. These patients do not meet the diagnostic criteria for IBS, functional constipation, functional diarrhea, or postprandial distress syndrome.

CLINICAL EVALUATION AND DIAGNOSTIC WORKUP

The diagnosis of IBS relies on a thorough patient history, physical examination, and limited laboratory testing. While not necessary for diagnosis, a brief psychosocial assessment should be performed in all patients. In most patients who fulfill Rome IV diagnostic criteria and for whom alarm features are absent, the need for diagnostic testing should be minimal; performing a battery of tests in all patients suspected of IBS is not warranted. However, focused diagnostic testing may be required to differentiate IBS from several conditions with mimicking symptoms when ambiguity is present. IBS mimics include inflammatory bowel disease, celiac disease, lactose and fructose intolerance, and microscopic colitis [3].

Clinical History

Abdominal pain is a hallmark of IBS; the absence of abdominal pain precludes the diagnosis of IBS. Pain can be present anywhere throughout the abdomen, although it is more common in the lower abdomen [3].

A history of disordered bowel habits (i.e., constipation, diarrhea, or both) should be identified, along with a temporal association with episodes of abdominal pain. Unpredictable bowel pattern (i.e., three or more different stool form types/week) reinforces the diagnosis of IBS-D. An increasing number of consecutive days without a bowel movement suggests a diagnosis of IBS-C.

Ask patients for specific information regarding bowel habits and stool characteristics, as this informs subtyping of their IBS. A diagnosis of unclassified IBS (IBS-U) is reserved for patients meeting IBS diagnostic criteria whose bowel habits cannot be accurately grouped into one of the three main subtypes; this group is uncommon. Difficulty in accurate subtyping can result from frequent changes in diet or medications or an inability to stop medications that affect GI transit. Subtyping should be based on the patient's reported predominant bowel habit on days with abnormal bowel movements. As noted, the BSFS should be used to record stool consistency [124].

Diagnosing patients with IBS-D or IBS-C is usually straightforward, but IBS-M can be more complex. A detailed history helps determine whether mixed bowel patterns originate from the underlying disease state or are a consequence of medical intervention. All prescription and over-the-counter medications and supplements with known influence on IBS symptoms should be considered. A stool diary helps identify patterns in the erratic bowel habits of many patients with IBS. Patients with IBS-M often report protracted periods when bowel movement is absent or appears with small, hard stools; this is followed by periods of multiple stools of variable consistency interpreted by patients as diarrhea. In most cases, this reflects IBS-C, and radiographic demonstration of fecal loading helps confirm clinical suspicion [5].

Non-Specific Symptoms

Common non-specific symptoms in IBS include abnormal stool frequency, abnormal stool form (BSFS types 1/2 or 6/7), excessive straining during defecation, urgency to defecate, feelings of incomplete evacuation, and mucus with bowel movements. Abdominal bloating is present in most patients with IBS and abdominal distention may be reported, but neither is required for an IBS diagnosis [3].

Patients with IBS frequently report that symptoms are induced or worsened by meals, although these symptoms are not specific to IBS. Many other functional GI (e.g., dyspepsia) and non-GI (e.g., migraine headaches, fibromyalgia, interstitial cystitis, dyspareunia) disorder symptoms are reported in patients with IBS; their presence supports an IBS diagnosis [3].

Physical Examination

A physical examination should be performed for every patient evaluated for IBS. This reassures the patient and helps exclude organic etiology. Physical examination frequently reveals tenderness in the left lower quadrant over a palpable sigmoid colon. A rectal examination is warranted to rule out rectal disease and abnormal function of the anorectal sphincter (e.g., paradoxical pelvic-floor contraction during a defecation attempt), which may contribute to symptoms of constipation [125]. The presence of ascites, hepatosplenomegaly, or abdominal mass warrants further evaluation. An anorectal examination is mandatory to identify anorectal causes of bleeding, evaluate anorectal tone and squeeze pressure, and identify dyssynergic defecation [3].

Differential Diagnosis

Several diseases should be considered in patients with IBS symptoms, including celiac disease, inflammatory bowel disease, giardiasis, and dyssynergic defecation. When detailed history taking, physical examination, and/or routine laboratory testing results make it crucial to rule out a disease that requires diagnostic tests or functional studies not available in primary care, referral to a specialist is indicated.

Celiac Disease

Patients with IBS symptoms have a fourfold increased risk of biopsy-proven celiac disease [5]. However, the prevalence of celiac disease in patients with IBS symptoms varies by region, with European studies, but not American studies, demonstrating a higher prevalence of the disease. Routine celiac disease screening in patients with IBS becomes cost-effective with prevalence ≥1%. Given the potential long-term consequences of a missed celiac disease diagnosis, clinicians caring for patients with IBS should have a low threshold of suspicion, especially in patients with IBS-D [5; 126].

Serologic tests for celiac disease should be performed in patients with IBS-D or IBS-M who fail empiric therapy. Upper GI endoscopy with duodenal biopsies should be performed if serologic tests for celiac disease are positive or clinical suspicion is high; duodenal biopsies can also identify tropical sprue, another mimic of IBS.

Microscopic Colitis

A small subgroup of patients with suspected IBS-D have microscopic colitis. Risk factors for microscopic colitis include age older than 50 years, nocturnal stools, weight loss, shorter duration of diarrhea, recent introduction of new medications, and comorbid autoimmune disease. When colonoscopy is performed in patients with suspected IBS-D, random colon biopsies should be obtained to rule out microscopic colitis [5; 126].

Inflammatory Bowel Disease

Inflammatory bowel diseases, like Crohn disease, can mimic IBS symptoms during acute inflammatory flares. Nerve and muscle changes can persist following acute inflammation, even in remission. The underlying mechanisms may include altered gut permeability and persistent low-level immune activation, shown by cecal biopsies from patients with inflammatory bowel disease in apparent remission with ongoing IBS symptoms. Other mechanisms may include persisting alterations in enteric nerves and serotonin signaling. This information can help identify patients with inflammatory bowel disease and persistent IBS symptoms who may respond better to dietary restriction and other IBS treatments than to escalated immunosuppression [87; 127; 128].

Because even low-grade chronic inflammation can alter gut permeability and sensitize visceral afferent neurons, leading to aberrant motility and visceral sensitization, inflammatory bowel disease should be considered in all patients with IBS symptoms. IBS criteria are met by more than 33% of patients with inflammatory bowel disease, but the proportion of patients with inflammatory bowel disease and overlapping IBS symptoms with alarm features is unclear [5].

The pragmatic question is how often inflammatory bowel disease is ultimately identified in patients with typical IBS symptoms who lack alarm features. A prospective U.S. study of more than 900 nonconstipated patients with IBS and healthy controls receiving colonoscopy found inflammatory bowel disease in less than 1% of patients with IBS and none in the controls. This argues against routine colonoscopy in patients with typical IBS symptoms who lack concerning features. Noninvasive biomarkers may be more cost-effective than colonoscopy for inflammatory bowel disease screening [5; 129].

Fecal calprotectin, a biochemical assay for intestinal inflammation, is a cost-effective choice in inflammatory bowel disease screening, although 33% of patients with inflammatory bowel disease and IBS-like symptoms show negative results. C-reactive protein levels of <0.5 mg/dL or fecal calprotectin levels of <40 mcg/g confer a ≤1% risk of inflammatory bowel disease in patients with typical IBS symptoms [5; 130]. However, inflammatory bowel disease was found to develop two to three years after initial IBS diagnosis at rates far exceeding population norms, despite negative colonoscopy findings [31].

The American Gastroenterological Association (AGA) recommends that either calprotectin or fecal lactoferrin and C-reactive protein be checked in patients without alarm features and with suspected IBS and diarrhea symptoms to rule out inflammatory bowel disease [220]. If inflammatory markers are mildly elevated but the probability of inflammatory bowel disease is low, testing should be repeated before performing colonoscopy (unless other indications for colonoscopy are present). Inflammatory markers are not useful in patients with constipation-predominant symptoms.

Giardiasis

Giardia is a relatively common enteric parasitic infection that causes subacute-to-chronic watery diarrhea often accompanied by bloating, urgency, and excess flatulence. Infection is acquired from contaminated water sources in geographic regions scattered throughout the United States. Fluctuating symptoms and chronicity are common, leading to psychological stress and social disruptions not unlike that experienced by patients with IBS. Examination of stool for the parasite has variable sensitivity, but stool tests that rely on detection of *Giardia* antigen or subunit ribosomal RNA are highly sensitive and specific. This is a curable cause of GI symptoms, as the condition can be easily and effectively treated.

Bile Acids Diarrhea

As noted, perfusion of bile acids into the colon stimulates water and electrolyte secretion and accelerates transit. Evidence of bile acid malabsorption may be present in up to 33% of patients with IBS-D symptoms. Clinicians can empirically assess for bile acid malabsorption by initiating a bile acid sequestrant trial. Several tests can identify such malabsorption but are not widely available in the United States [5; 92].

Dyssynergic Defecation

Dyssynergic defecation is an under-recognized, constipation-associated condition characterized by an inability to coordinate abdominal wall, anal sphincter, and pelvic floor muscles for normal defecation. Symptoms are non-specific and include abdominal pain, discomfort, and bloating. Intervention with biofeedback can improve bowel and abdominal symptoms. Thus, patients with medically refractory IBS-C symptoms should be referred to a specialist for evaluation of dyssynergia by digital rectal examination, anorectal manometry, balloon expulsion testing, or anorectal imaging [131; 132; 133].

Laboratory Studies

There is no specific laboratory test that defines the presence of IBS; laboratory evaluation is used selectively to screen for other disorders in the differential diagnosis, principally in patients with IBS-D. In 2019, the AGA published a guideline to aid clinicians in choosing appropriate laboratory tests to exclude other diagnoses in the patient with functional diarrhea and IBS-D [209]. This guideline is applicable for the typical patient with chronic "watery" diarrhea of at least six weeks' duration, and is not intended to guide the evaluation of patients with a more complicated clinical profile, such as bloody diarrhea, recent foreign travel to regions endemic for enteric pathogens, or family history of inflammatory bowel disease or cancer. The AGA recommendations for laboratory testing in patients presenting with chronic diarrhea (IBS-D) are [209]:

- Either fecal calprotectin or fecal lactoferrin to screen for inflammatory bowel disease (threshold value: 50 mcg/g for calprotectin to optimize sensitivity)
- *Giardia* antigen test or polymerase chain reaction to screen for giardiasis
- Testing for celiac disease with IgA tissue transglutaminase and a second test to detect celiac disease in patients with IgA deficiency
- Consider testing for bile acid diarrhea (or an empiric trial of a bile acid binder)

The AGA suggests against the use of erythrocyte sedimentation rate or C-reactive protein to screen for inflammatory bowel disease and against testing for ova and parasites (other than *Giardia*) if there is no travel history or recent immigration from high-risk areas [209].

On initial evaluation, most patients with IBS should have a complete blood count to rule out anemia or screen for systemic signs of infection. In the absence of alarm symptoms or suspicion of abnormalities that other laboratory testing can confirm, no other testing is needed for diagnosis. However, the presence of alarm criteria requires further testing specific to the index alarm finding—colonoscopy in most cases [3; 44].

Colonoscopy is indicated in the presence of alarm symptoms, family history of colorectal cancer, or persistent diarrhea that has failed empiric therapy. Biopsies of different segments of the colon may be required in patients with chronic diarrhea to rule out microscopic colitis. Colorectal cancer screening colonoscopy is indicated in patients 50 years of age or older (or 45 years of age or older in African Americans) in the absence of warning signs based on national recommendations.

With failure of empiric therapy, other diagnostic options in limited use include [3]:

- Scintigraphic evaluation (75SeHCAT test)
- Postprandial serum C4 (7a-hydroxy-4-cholesten-3-one)
- FGF19

Breath tests to rule out carbohydrate malabsorption may be useful in some patients with IBS symptoms and persistent diarrhea.

Alarm Features

Concerning features that may suggest organic disease require assessment. Although the presence of these features may identify patients with organic disease, most will have negative evaluation findings, and concerning features are valuable for their negative (not positive) predictive value. IBS can be confidently diagnosed in patients who meet symptom-based criteria and lack concerning features, because extensive diagnostic testing is infrequently positive. However, the perspective of IBS as a diagnosis of exclusion remains widespread, and many healthcare professionals are uncomfortable relying solely on symptom-based criteria for its diagnosis [5; 134].

Alarm criteria requiring further testing to rule out organicity include [3; 44]:

- Personal or family history of colorectal cancer, intestinal polyposis, inflammatory bowel disease, or celiac disease
- Symptom onset after 50 years of age
- Recent changes in bowel movement habit

Additional signs and symptoms that may suggest organicity are:

- Nocturnal symptoms
- Fever
- Anemia
- Unintended weight loss not explained by other causes
- Fecal blood in the absence of documented bleeding hemorrhoids or anal fissures
- Severe abdominal pain
- Palpable abdominal mass, visceromegalias, or abnormal digital rectal examination on physical exam

Psychosocial Assessment

As discussed, psychosocial factors influence physiologic functioning of the GI tract (including motility, sensitivity, and barrier function), mediate pain experience and symptom behavior of the patient, and impact treatment selection and clinical outcome [15]. This makes psychosocial assessment a vital part of the evaluation of patients with IBS symptoms.

Primary care clinicians and gastroenterologists can use psychosocial screening to identify patients at risk for refractory symptoms, poor treatment response, or low quality of life. When overt psychopathology or moderate-to-severe symptoms are absent, visceral-specific anxiety, catastrophizing, somatization, and quality of life can be assessed to determine if comprehensive evaluation by a health psychologist or psychiatrist is indicated [55].

Clinicians should consider a brief psychosocial assessment for each patient with functional GI disorder, with the precondition that a satisfactory patient-clinician relationship is established earlier in the evaluation. A few specific questions on key psychosocial processes can be woven into routine history taking. If a patient asks about the relevance of this inquiry, a truthful response is, "I always ask my patients these questions as part of my initial assessment—it helps me determine the best way to help. The items may or may not apply to you." This psychosocial assessment will only be satisfactory if the patient is able to speak freely, which requires privacy, a lack of judgment or stigma, and sufficient time. Sensitive areas of discussion include abuse history, depressed mood, possible suicidal thoughts, and the nature of intimate relationships. These may require a second appointment for a full assessment.

The clinician should provide feedback about results of the overall evaluation and discuss treatment options, which can include medical and psychosocial approaches [55]. Consider referring patients with severe symptoms, previous treatment failure, poor treatment adherence, or marked disability to a clinician with special training in psychosocial assessment [55].

Changes in Symptom Severity, Frequency, or Treatment Response

When a plausible explanation for a change in symptoms or treatment response in patients with an established IBS diagnosis is lacking, it is important to assess for an underlying causal condition. Following a new physical examination, time since the last diagnostic workup should be considered. Changes in epidemiologic characteristics of the family should be assessed and recorded. IBS can include phases where symptom severity changes, and patients may perceive they have an inadequately explored organic disease. With these considerations, additional diagnostic testing should generally be limited to the presence of alarm symptoms or signs [44].

TREATMENT

Treatment of IBS should be directed at the dominant symptom type and severity [3]. In this section, interventions for all IBS subtypes (e.g., lifestyle, psychological interventions, dietary, antidepressants) are discussed first, followed by therapeutic options specific to dominant symptom type (i.e., constipation, diarrhea, abdominal pain).

THE THERAPEUTIC RELATIONSHIP AND TREATMENT ADHERENCE

IBS patient management begins by explaining the condition, providing reassurance of the benign natural history, and educating the patient about the benefits and safety of diagnostic tests and treatment options [3]. Clinical experience suggests that providing the patient with a plausible disease model (e.g., "brain-gut disorder") and accepting patient symptoms and distress as real instead of dismissing them as "psychosomatic" helps to establish a positive therapeutic relationship. An approach that acknowledges the disease, educates the patient about the disease, and reassures the patient may improve treatment outcomes [125].

Steps to Enhance the Therapeutic Relationship

Healthcare professionals who repeatedly perform unnecessary diagnostic studies to rule out pathologic disease, dismiss patient concerns, or do not collaborate effectively in patient care can promote a vicious cycle of symptom anxiety and health care seeking [2]. Effective provider-patient relationships can improve patient satisfaction, treatment adherence, symptom reduction, and other health outcomes. General guidelines can help optimize this relationship with patients with IBS [2]. Patient satisfaction is based on a perception of healthcare providers' humaneness, technical competence, interest in psychosocial factors, and provision of relevant health information; over-emphasis on biomedical issues can have a negative effect. In addition to verbal communication, engagement involves nonverbal communication such as good eye contact, affirmative nods, a gentle tone of voice, close interpersonal distance, and creation of a partner-like interaction.

It is important to conduct the patient history using a nondirective, nonjudgmental, patient-centered approach. This involves active listening and asking questions based on the patient's thoughts, feelings, and experiences, instead of a preset agenda of questions. A good first step is to inquire regarding the reason for the appointment. Immediate reasons for a patient's visit may include [135]:

- New or exacerbating factors (e.g., dietary change, concurrent medical disorder, side effects of new medication)
- Personal concern about a serious disease (e.g., recent family death)
- Personal or family stressors (e.g., recent or anniversary of death or other major loss, abuse event, or history)
- Worsening or development of psychiatric comorbidity (e.g., depression, anxiety)
- Impairment in daily function (e.g., recent inability to work or socialize)
- A hidden agenda (e.g., opioid or laxative abuse, pending litigation, disability claims)

The next step is a careful physical examination and investigation. Although this obviously assists in diagnosis and assessment of new complaints, a well-conducted physical examination itself has therapeutic value [136].

In the course of clinical assessment, it is important to pay attention to patient concerns and understanding of their illness and to provide an explanation of the disorder that takes into consideration the patient's own perspective and beliefs about their condition. When plausible, one should point out the link between stressors and symptoms consistent with patient's views. Many patients are unable or unwilling to associate stressors with illness, but most understand the impact of illness-related stress on their emotional state.

Patients should be given therapeutic options and be involved in treatment decision-making. When possible, treatment recommendations should be consistent with patient interests. Identifying and responding realistically to the patient's expectations for improvement can strengthen rapport. However, it is also important to set consistent limits, especially as related to pain management and opioid use.

Finally, patients should be reassured that care will continue and that they should expect an ongoing relationship. It can help to let patients know that many treatment options can be explored to help control IBS.

Steps to Enhance Therapy Adherence

Adherence is essential for the effectiveness of prescribed therapy, including dietary measures, lifestyle changes, and pharmacotherapy. A therapy regimen alone is often insufficient unless the patient understands and accepts the approach and agrees to follow it. This highlights the importance of a trust-based therapeutic relationship that promotes cooperation and empowers patient participation in decision-making and responsibility for self-care [44].

In addition to consideration of best-available therapeutic options, the following measures can facilitate patient engagement and adherence [44]:

- Prescribing therapeutic regimens with the least number of effective daily doses
- Providing simple, easy-to-understand written information and reminders
- Providing adherence "diaries" to the patient
- Including information on the pathophysiology of the condition (according to education level) in patient education
- Including family members and caregivers who can positively reinforce patient behavior

The importance of regularity should be stressed for constipation management. Some patients only use medication intermittently for exacerbations, which is less effective. Other patients avoid laxatives altogether due to false beliefs that laxatives induce dependence or may be ultimately dangerous.

LIFESTYLE MODIFICATION

Limited data suggest that IBS symptoms may be improved by lifestyle modifications that include exercise, stress reduction, and good sleep habits [3]. Greater evidence supports dietary interventions.

Increased physical activity in patients with IBS has been found to improve GI symptoms and help protect against symptom deterioration [137]. In one study, exercise for 12 weeks significantly improved symptoms and extra-intestinal manifestations of IBS in 102 patients, while another 12-week exercise trial significantly improved constipation but not other IBS symptoms [137; 138]. In adolescent patients with IBS, one hour of yoga daily for four weeks significantly improved symptoms [139].

Other recommendations that may improve IBS symptoms include [118]:

- Judicious water intake (particularly for patients with IBS-C)
- Caffeine avoidance
- Legume avoidance

The National Collaborating Centre for Nursing and Supportive Care recommends drinking at least eight cups of fluid per day, especially water or other non-caffeinated drinks, for example herbal teas. Tea and coffee should be limited to three cups per day.

(https://www.nice.org.uk/guidance/cg61. Last accessed November 18, 2022.)

Level of Evidence: Consensus Statement/ Expert Opinion

Poor quality of sleep is relatively common in patients with IBS, and studies have shown that sleep difficulties predict next-day exacerbations, fatigue, and depressed mood [140]. Researchers have suggested autonomic nervous system dysregulation may be a common factor underlying both IBS symptoms and sleep disturbances. As such, patients should try to get enough sleep (at least seven to eight hours per night) and should keep good sleep hygiene (e.g., avoidance of electronics in the bedroom, going to sleep and rising at the same time every day).

Perceived high stress levels can also increase the risk for IBS exacerbations and increased symptoms [141]. Avoidance of high-stress situations, when possible, is recommended. However, psychological interventions may also help provide effective stress-coping strategies.

Dietary Interventions

Most patients with IBS are aware that their gastrointestinal symptoms are precipitated or made worse by eating certain foods. In 2022, the AGA published a clinical practice update on the role of diet in IBS management based on mounting evidence supporting diet modifications as a primary treatment for IBS symptoms [215]. To optimize patient education and clinical response, the AGA recommends referral to a registered dietician nutritionist for patients willing to collaborate and for patients who are not able to implement beneficial dietary changes on their own. Patients should attempt specific IBS diet interventions for a predetermined length of time (e.g., –four to six weeks); if there is no clinical response, the diet intervention should be abandoned in favor of another treatment alternative (e.g., different diet, medication, other mode of therapy) [215].

Dietary and Supplemental Fiber

Dietary fiber supplementation has long been the foundation of treatment in all patients with IBS, and IBS guidelines have consistently recommended dietary fiber by increasing fiber-rich foods or adding soluble fiber (usually *Psyllium* seed, but polycarbophil compounds may produce less flatulence) [44; 118]. Soluble fiber is found in psyllium, corn fiber, calcium polycarbophil, methylcellulose, oat bran, and the flesh of fruits and vegetables; insoluble fiber is found in wheat bran, whole grains, and fruit and vegetable skins and seeds [215]. Guidelines recommend the use of soluble (but not insoluble) fiber for the treatment and improvement of global IBS symptoms. This recommendation is based on a systematic review and meta-analysis of 15 random-

ized controlled trials showing that soluble fiber may benefit patients with IBS, while causing only minor adverse effects [215].

While evidence indicates that poorly fermentable, soluble fiber has modest benefits in reducing global IBS symptoms in patients with IBS-C with mild constipation, insoluble fiber may worsen abdominal pain and distension and has little benefit in patients with IBS-D. Wheat bran, in particular, can exacerbate problems of abdominal distention, abdominal pain, and flatulence and should be avoided [3; 5; 44]. If fiber is indicated, initiate soluble fiber at a very low dose and gradually increase to total daily intake of 20–30 g [5].

Gluten Restriction

Dietary restriction of gluten may improve symptoms in some patients with IBS. Two small prospective studies in patients with IBS, in which celiac disease was carefully excluded, demonstrated global symptom improvement [97; 98].

Dietary FODMAP Restriction

Numerous short-chain carbohydrates, including lactose, fructose, and polyols, can provoke IBS symptoms [84; 143; 144]. These short-chain fermentable carbohydrates are collectively termed FODMAPs, and there is direct evidence (using magnetic resonance imaging) that some FODMAPs may induce IBS symptoms via increased small bowel water content or increased colonic gas production [84; 143; 144].

FODMAPs promote poor absorption in the small bowel and rapid fermentation in the colon. FODMAP is an acronym for [87]:

- **F**ermentable
- **O**ligosaccharides (e.g., fructo-oligosaccharides, galacto-oligosaccharides, fructans, raffinose, inulin)
- **D**isaccharides (e.g., lactose, sucrose)
- **M**onosaccharides (e.g., fructose)
- **A**ND
- **P**olyhydric alcohols (e.g., sorbitol, mannitol, xylitol, maltitol)

The most common sources of FODMAPs in the western diet are wheat, onions, fruit in which fructose exceeds glucose (e.g., apples, pears), and processed food. Dairy products are important in those with lactose malabsorption.

True lactose intolerance may induce IBS-like symptoms, but only with relatively high lactose loads (20 g) that are easily avoidable. Psychological factors have a major influence on symptomatic responses to lactose intake [145; 146].

Fructose is a monosaccharide abundantly present in many processed foods. The small bowel has a relatively limited absorptive capacity that particularly affects free fructose—the fraction in excess of the glucose that facilitates fructose absorption. High fructose loading can induce symptoms even in healthy individuals.

Polyols such as sorbitol, mannitol, and xylitol are naturally present in many fruits and vegetables and are added as artificial sweeteners to processed food products and pharmaceuticals. Polyols tend to induce bowel discharges from their stimulant effect on intestinal motility.

Dietary FODMAP restriction is associated with reduced fermentation and significant symptom improvement in some patients with IBS. In a randomized, controlled, single-blind cross-over trial, patients with IBS who had not previously tried dietary manipulation reported significant reduction in overall GI symptom scores compared with those on a standard Australian diet [87]. The complexity of the FODMAP diet makes implementation difficult, but this may be overcome by excluding only the major sources of FODMAPs (e.g., wheat, onions, dairy), avoiding processed food, and not focusing on items with small specific contribution [87]. Adding a gluten-free diet to patients with IBS already on a low FODMAP diet does not appear to offer additional benefit [147; 148; 149]. The AGA 2022 guideline recommends the low-FODMAP diet as the most evidence-based diet intervention for IBS [215].

Probiotics

Manipulation of intestinal microbiota has promise as a potential therapy for gut dysbiosis to ameliorate symptoms of IBS and restore health. The concept of probiotics is more than 100 years old, and modern research methods are establishing empiric support for the perceived benefits of probiotic bacteria, which mainly include *Lactobacillus* and *Bifidobacterium* species [150].

Probiotics have been generally defined as live microorganisms that upon ingestion in specific and sufficient numbers confer unspecified health benefits to the host [216]. Selection is based on ability to survive in the GI tract, adhere to intestinal epithelium, and modulate intestinal flora. Potential benefits attributed to probiotics include improved general gut health; prevention of intestinal overgrowth and translocation (infection) of gut pathogenic bacteria; modulation or stimulation of immune responsiveness via immune cell proliferation; enhanced phagocyte activity; and increased production of immunoglobulin A [44; 151].

The reported potential benefit of probiotics in managing IBS could occur through multiple mechanisms. *Bifidobacterium infantis* 35624 led to significant improvements in abdominal pain/discomfort, bloating/distention, and/or bowel movement difficulty (vs. placebo) in two randomized controlled trials of patients with IBS [152; 153]. A 2016 meta-analysis that included 43 clinical trials using different products found probiotics to offer benefits for global IBS symptoms, pain, bloating, and flatulence. However, the reliability of these findings is limited by the variability of IBS diagnostic criteria and symptom measurement methods in published randomized controlled trials [154]. Despite growing scientific and commercial interest, studies assessing probiotics for the treatment of IBS and other GI disorders have been varied, including differences in the strain and dose of microbes used, as well as the research methodology and differences in reporting of end points and outcomes [216].

In 2020, the AGA published guidelines on the use of probiotics for several gastrointestinal disorders, including IBS. After reviewing a total of 76 randomized controlled trials that used 44 different probiotic strains or combination of strains, the AGA made no recommendations for the use of probiotics in children and adults with IBS. The review found that many studies examining this question are marked by significant heterogeneity in study design, outcome, and probiotics used [217].

Prebiotics/Symbiotics

Prebiotics are food products that promote proliferation of bifidobacteria and other species potentially associated with anti-inflammatory effects (e.g., oligofructose, inulin, galacto-oligosaccharides, lactulose, breast milk oligosaccharides). Prebiotics do not seem particularly effective in IBS, possibly due to fermentation products that may themselves stimulate IBS symptoms. Trials for prebiotics are few in number, and no definite conclusions can be drawn [84].

Symbiotics aim to simultaneously produce synergic pro- and prebiotic effects, but evidence has not substantiated their theoretical benefits in IBS. Further evidence is required to establish the role of prebiotics or synbiotics in IBS [84].

PSYCHOLOGICAL INTERVENTIONS

As discussed, psychological factors can amplify pain perception and experience, and strong empirical evidence confirms that pain experience is powerfully influenced by pain catastrophizing, fear avoidance behavior, self-efficacy, lack of perceived control, and passive pain coping. Other psychosocial research has found that depression and anxiety mediate the effect of pain on impaired function and that trauma history can negatively influence pain experience, pain and stress coping, and the clinician-patient relationship. This all supports the utility of psychological interventions in IBS management [62; 155; 156].

Psychological interventions address the cognitive-affective and psychosocial variables that interact with, reinforce, and perpetuate the physiologic factors that are involved in symptom expression, symptom severity, and impact of the disease on other health outcomes (e.g., quality of life, health care use) [55].

Cognitive-Behavioral Therapy

CBT refers to a family of psychological treatments rather than a specific technique. CBT is derived from behavior theories that focus on learning processes and cognitive theories that emphasize faulty cognitions or thinking processes. These same learning processes are used to help patients gain control and reduce symptoms of IBS. Cognitive theory views external events, cognitions, and behavior as interactive and bidirectional, with primary emphasis on how patients process information about their environment, self, and the future. Cognitive factors, especially the way people interpret or think about stressful events, can intensify the impact of events on patient response. Emotional, physiologic, and behavioral responses to life events will be problematic to the extent that thought processes are faulty. Clinically modifying patient thinking can change behavior and emotional and physical well-being. Cognitive changes can occur by teaching patients to systematically identify cognitive errors generated by automatic thinking, or by providing experiential learning that systematically exposes patients to the situations that cause discomfort [55; 157].

Unlike traditional, insight-oriented "talk therapy," which identifies the root causes of a problem, CBT focuses on teaching people how to control their current problems by identifying the thoughts and behaviors that are maintaining them. CBT requires active patient participation during and between sessions and patient responsibility for learning symptom self-management skills. With IBS, CBT can include a combination of techniques such as self-monitoring, cognitive restructuring, problem solving, exposure, and relaxation methods [55].

Self-Monitoring

Self-monitoring is the ongoing, real-time recording of problem behaviors. In IBS, the focus of self-monitoring is internal and external triggers and the thoughts, somatic sensations, and feelings that usually accompany flare-ups. Self-monitoring provides clinically relevant information with which to structure treatment and serves as a useful therapeutic strategy by increasing patient awareness of triggers and contributing factors [55].

Cognitive Strategies

Cognitive strategies are designed to modify thinking errors that bias information processing (e.g., tendencies to overestimate risk and magnitude of threat or underestimate one's ability to cope with adversity). These self-defeating beliefs are clinically important because they are believed to moderate excessive stress experiences. Negative beliefs are identified, and the patient works with the healthcare provider to challenge and dispute them. This involves examining the accuracy of beliefs in light of available evidence and replacing biased beliefs with more logical and constructive cognitions [55].

Problem Solving

Problem solving refers to an ability to define problems, identify solutions, and verify their effectiveness once implemented. The intervention is rooted in the problem-solving model of stress, which acknowledges that a causal relationship exists between health and stressors. Using this model, the health or mental health professional teaches patients how to effectively apply the steps of problem solving to actively cope with stress [55; 158].

Relaxation Procedures

Various relaxation techniques are effective in managing IBS symptoms, and relaxation procedures have long been a staple of psychological treatments for functional GI disorders. These techniques, including progressive muscle relaxation, breath work, and meditation, are designed to directly modify autonomic arousal believed to aggravate GI symptoms [159].

Progressive muscle relaxation training involves systematically tensing and relaxing selected muscle groups throughout the body, from forehead to feet. This exercise helps patients dampen physiologic arousal and achieve a sense of mastery of physiologic self-control over previously uncontrollable and unpredictable symptoms [55; 160].

In breathing retraining, the patient is taught to take slow, deep breaths and focus on bodily sensations during exhalation. This technique is based on the idea that patients with stress-related physical ailments develop inefficient respiratory patterns (e.g., shallow chest breathing), which, if chronic, can intensify physiologic arousal and increase somatic complaints [55; 161].

Meditation is a self-directed practice that can emphasize focused breathing and mindfulness. Mindfulness is defined as purposefully paying attention in the moment without judgement. This nonjudgmental acceptance of thought processes allows the practitioner to achieve a state of calmness, physical relaxation, and psychological balance. In mindfulness meditation for IBS, the patient disengages him/herself from the ruminative thoughts considered core aspects of pain and suffering by developing a nonreactive, objective, present-focused approach to internal experiences and external events as they occur [55; 162]. Small studies have indicated that engagement in a mindfulness-based stress reduction program can ameliorate IBS symptoms, reduce stress, and improve patients' quality of life, with continued improvements evident after six months [163].

Hypnosis

In hypnosis, a therapist typically induces a trance-like state of deep relaxation and/or concentration using strategically worded verbal cues suggestive of changes in sensations, perceptions, thoughts, or behavior. Most hypnotic suggestions are designed to elicit feelings of improved relaxation, calmness, and well-being. Hypnotic suggestions in IBS are "gut directed," meaning suggestions are conveyed that are incompatible with aversive visceral sensation. Hypnosis might include a suggestion to feel a sense of warmth and comfort spreading throughout the abdominal area [55; 164]. Hypnosis has shown some benefit in decreasing IBS symptoms in adults [165].

Exposure Therapy

Exposure therapy is designed to reduce catastrophic beliefs about IBS symptoms, hypervigilance for IBS symptoms, fear of IBS symptoms, and/or excessive avoidance of unpleasant visceral sensations or situations by helping patients confront maladaptive thoughts and beliefs in a systematic manner. Exposure can include interoceptive cue exposure (i.e., the patient repeatedly provokes unpleasant sensations) or situational/in vivo exposure (i.e., feared situations or activities are confronted). Through exposure treatments, patients learn the stimuli that led to fear and avoidance are neither dangerous nor intolerable and that fear will subside without resorting to avoidance, a behavior that reinforces fear and hypervigilance in the long-term [166; 167]. In an experimental study of 13 patients with IBS, 70% improved on measures of GI symptoms, pain catastrophizing, and quality of life following 12 sessions of exposure therapy [168].

Efficacy of Psychological Treatments

Periodic meta-analyses conducted over the past two decades have consistently demonstrated that psychological therapies, as a class of treatments, are at least moderately effective for relieving symptoms of IBS when compared with a pooled group of control conditions. The Internet has been used as a treatment delivery platform to give a larger proportion of patients with functional GI disorder access to, and engagement in, therapy than would have been feasible through clinic-based treatment alone [169; 170; 171].

A 2016 meta-analysis investigated the duration of sustained benefit gained from psychological therapy in reducing GI symptoms in patients with IBS. Forty-one trials recording data from 2,290 subjects (1,183 assigned to therapy, 1,107 assigned to a control condition) were analyzed. Compared with a mixed group of control conditions, psychological therapies

had a medium size effect on reducing GI symptom severity immediately after treatment. On average, subjects receiving psychotherapy had greater post-therapy reduction in GI symptoms than individuals assigned to a control condition. After short-term follow-up (1 to 6 months after treatment) and long-term follow-up (6 to 12 months after treatment), this beneficial effect remained significant and medium in magnitude [172].

For the most part, the efficacy of psychological therapies for IBS has been demonstrated from studies conducted as freestanding clinical trials; less clear is the effectiveness of psychotherapy approaches within the context of general clinical practice. To assess this further, a systematic review was made of the types and effects of psychological treatments for IBS conducted in gastroenterology clinic settings. In an analysis of seven eligible studies comparing psychological treatments to controls, IBS symptoms improved significantly among patients in cognitive and behavioral therapies, mindfulness-based stress reduction, guided affective imagery, and emotional awareness training [210].

ANTIDEPRESSANT MEDICATIONS

Although antidepressants are used extensively in the treatment of IBS and other functional GI disorders, the accumulated clinical experience, lack of other effective treatment options, and evidence from other functional somatic syndromes such as fibromyalgia make these agents viable options for treating pain and improving quality of life in patients with IBS. In general, antidepressant medications should be reserved for patients with moderate-to-severe symptoms with significant impairment of quality of life for which other first-line treatments have not been sufficiently effective [173; 174].

Choice of Agent

The choice of antidepressant agent is determined by the patient's predominant symptoms, disease severity, presence of comorbid anxiety or depression, prior experience with medications in the same class, and patient and prescriber preference. The three broad antidepressant classes most often used in IBS are tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), and serotonin-noradrenalin reuptake inhibitors (SNRIs) [55].

Tricyclic Antidepressants

TCAs such as amitriptyline, imipramine, desipramine, doxepin, and trimipramine are the most widely used psychotropic agents for treating neuropathic (e.g., postherpetic neuralgia, diabetic neuropathy) and functional (e.g., fibromyalgia) pain syndromes. Their analgesic effect is thought to be independent of antidepressant mechanisms and effects because TCAs can benefit patients with diverse pain syndromes in whom psychopathology is modest or absent and because they are often effective for pain at low (sub-psychiatric) doses [106; 175; 176].

In general, TCAs are the first antidepressant choice for pain in non-constipated patients with IBS due to their dual mechanism of action (serotonin and norepinephrine reuptake inhibition). Nortriptyline or desipramine is better tolerated than amitriptyline or imipramine due to fewer anti-histaminergic and anti-cholinergic effects. The usual starting dose is 25–50 mg at night and can be titrated up as needed up to about 150 mg/day, while carefully monitoring side effects and/or blood levels. Typically, lower doses than the full antidepressant dose are effective for visceral pain if no psychiatric comorbidity is present [55].

In one study, amitriptyline 10 mg/day in patients with IBS-D significantly improved overall IBS symptoms, reduced frequency of loose stool and feelings of incomplete defecation, and led to complete response (remission) in some [165; 177].

SSRIs

SSRIs are less effective for pain and are less commonly prescribed as monotherapy for IBS. Review papers have arrived at different conclusions concerning SSRI utility in IBS treatment, with some authors concluding no convincing evidence has been reported for functional GI disorders and others reporting beneficial effects for overall IBS symptoms [3; 93; 165].

EVIDENCE-BASED PRACTICE RECOMMENDATION

The American Gastroenterological Association (AGA) suggests against using selective serotonin reuptake inhibitors for patients with IBS.

(https://www.gastrojournal.org/article/S0016-5085(22)00391-2/fulltext. Last accessed November 18, 2022.)

Strength of Recommendation/Level of Evidence: Conditional recommendation/low-quality evidence

However, SSRIs are considered useful in patients with high levels of anxiety that contribute directly to IBS exacerbations and symptom severity. SSRIs and SNRIs have a more narrow therapeutic range, and therefore, the doses used for the treatment of pain are closer to the doses used for mood and anxiety disorders. Starting doses are usually within the lower range of the psychiatric dose (e.g., citalopram 20 mg or duloxetine 30 mg) and titrated up as needed [173; 174; 178].

A systematic review of SSRIs found benefits over placebo for overall IBS symptoms. Several clinical characteristics, including the predominant stool complaint, presence of insomnia, or comorbid anxiety, can influence antidepressant selection for individual patients with IBS [165].

SNRIs and Other Psychotropics

For SNRIs, especially venlafaxine, higher doses (≥225 mg) are usually required to attain effective analgesia because the noradrenergic mechanism of action is only evident at these doses. If nausea and weight loss are concerns, the addition of a low dose (15–30 mg) of mirtazapine can be helpful.

Atypical antipsychotics, such as quetiapine, are only recommended for patients with severe, refractory IBS, especially if severe anxiety and sleep disturbances are also present and the patient has failed to respond to other centrally acting agents. A low starting dose of 25–50 mg is recommended and can be titrated up as required [173; 174].

Augmentation of Therapy

Augmentation, or the use of a combination of drugs from different classes in submaximal doses instead of one drug at a maximal dose, is common in psychiatry and is increasingly used in the treatment of functional GI disorders. Examples of augmentation include adding buspirone to an SSRI, TCA, or SNRI to enhance therapeutic effect, or adding a low-dose antipsychotic (e.g., quetiapine) to a TCA or SNRI to reduce pain and anxiety and improve sleep. If there is a component of abdominal wall pain associated with the GI pain, pregabalin or gabapentin can be added to a TCA or SNRI [173; 174].

Combination Antidepressant and Psychological Treatment

Combining antidepressants with psychological therapy can be an effective augmentation strategy. Antidepressants can improve pain and vegetative depression symptoms, and psychological therapy improves higher cortical functioning, including coping, reappraising maladaptive cognitions, and adapting to previous losses and trauma. Psychotherapy can optimize medication adherence, while antidepressants can sufficiently increase physical and psychic energy to improve the level of engagement in therapy. The difference in effect size with combined treatment can exceed 50% compared to either treatment alone [106; 179; 180; 181].

Although drugs work faster and are readily available, psychological treatments have several advantages. They are safe and effective, their effects persist beyond the duration of the treatment, and they may be more cost-effective. Potential barriers to the use of psychological approaches in the treatment of IBS are a longer treatment duration, the need for patient motivation, and limited availability and access to a mental health professional trained in IBS treatment [55; 182].

Adherence

Careful patient selection, initiation at a low dose with gradual escalation, monitoring for side effects, and a good patient-clinician relationship are important for medication adherence and, by extension, therapeutic response. In particular, eliciting and addressing any potential concerns/barriers to taking psychotropic medications for IBS, discussing potential side effects, setting realistic expectations, and involving the patient in decision making result in improved adherence [55; 174].

DIARRHEA-PREDOMINANT IBS

Chronic diarrhea in IBS is usually associated with a non-infectious cause, and symptomatic drug therapy is indicated when definitive treatment is unavailable. Pharmacologic agents for IBS-D are diverse in mechanism of action, and prescribing these agents requires proper diagnosis and differential diagnosis in order to ensure effectiveness [183]. In 2022, the AGA reviewed pharmacologic therapy and published updated guidelines for treatment of IBS-D [218].

Mu Opioid Receptor Agonists

Loperamide is a synthetic, peripheral-acting mu opioid receptor agonist with limited ability to penetrate the blood-brain barrier (and therefore limited abuse potential). It decreases peristaltic activity, inhibits secretion, increases water and ion absorption, reduces colonic transit, and increases resting anal sphincter tone. This results in reduced fluid and electrolyte loss and improved stool consistency [93; 183]. Loperamide is available over the counter.

Diphenoxylate is another mu opioid receptor agonist, but unlike loperamide, it can cross the blood-brain barrier and is therefore combined with atropine to reduce abuse potential. Both of these agents are effective in reducing diarrhea in general, but research for the treatment of IBS-D is not well developed [93].

Several small randomized controlled trials of loperamide in IBS-D have shown reduced bowel frequency and improvements in stool consistency, urgency, and subjective overall response. Pain outcomes were mixed, with reduced pain intensity or increased nightly abdominal pain both reported in separate trials [3; 183]. However, loperamide may improve quality of life by allowing the planning of trips and socializing, which anxious patients with IBS-D often avoid for fear of fecal urgency or even incontinence [87].

Adverse effects with loperamide or diphenoxylate are rare, but include bladder dysfunction, glaucoma, and tachycardia. These may be more likely with diphenoxylate due to the atropine constituent [93].

Bile Acid Binders (Sequestrants)

As discussed, the underlying pathophysiology in some patients with IBS-D is bile acid perfusion into the colon, and bile acid sequestrants are used as treatment for these patients. Cholestyramine is the agent generally considered first-line treatment for IBS-D with bile acid diarrhea [3; 183]. Other options include colesevelam and colestipol. Cholestyramine granules are often poorly tolerated due to poor taste and adherence to the teeth [93].

Nonabsorbable Antibiotics

Antibiotics have traditionally been used as adjunctive IBS treatment. However, they are associated with systemic side effects, and there are concerns of promoting antibiotic-resistant microbes [184].

Rifaximin is a synthetic antibiotic derived from rifamycin and has anti-microbial activity against Gram-positive, Gram-negative, aerobic, and anaerobic bacteria. It is not absorbed by the intestinal mucosa, allowing intraluminal activity without systemic circulation and effects [185]. Rifaximin targets the GI tract to reduce gas-producing bacteria and alter the predominant bacterial species; it may also reduce mucosal inflammation and visceral hypersensitivity [93].

In 2015, rifaximin was approved by the FDA for the treatment of IBS-D in adults [93]. Clinical trials have demonstrated that rifaximin improved IBS-associated symptoms of bloating, flatulence, stool consistency, and abdominal pain. The drug showed a side-effect profile similar to placebo. Some patients experience relief of IBS symptoms after a course of rifaximin, while others require retreatment at the same dosage [184; 186]. Improvement in symptoms relative to placebo showed a gradual reduction over time, but significant improvement persisted for 10 weeks after the treatment course [3]. The usual dosage is 550 mg three times per day for 14 days [93].

The AGA suggests using rifaximin (over no drug treatment) in patients with IBS-D.

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Strength of Recommendation/Level of Evidence: Conditional recommendation/moderate-quality evidence

Clinical experience suggests that many rifaximin responders eventually develop recurrent IBS symptoms. Data from re-treatment patients suggest that second and third courses produce efficacy similar to the initial course. The role of other antibiotics in IBS treatment remains unknown, but antimicrobial resistance with repeated courses of systemically absorbed antibiotics is a concern [5]. Overall, rifaximin appears to be safe and beneficial as a management option for IBS-D, although optimal dosing and treatment duration and potential resistance require further study [184; 186].

5-HT3 Receptor Antagonists

Serotonin (5-HT) plays an important physiologic and pathophysiologic role in regulating GI function [187]. As such, 5-HT3 receptor antagonists (5-HT3RAs) can be effective treatment for IBS-D by slowing transit, reducing bowel frequency, normalizing stool consistency, and reducing urgency—a key symptom that impairs quality of life in patients with IBS-D [87].

Randomized controlled trials have found the potent, selective 5-HT3RAs alosetron and cilansetron may be effective in the treatment of IBS-D. However, alosetron was voluntarily withdrawn due to postmarketing reports of ischemic colitis (a potentially serious class-wide adverse event) and complications of constipation, while cilansetron was never marketed [187]. Alosetron was subsequently reintroduced to market and is currently available for women with severe IBS-D refractory to conventional therapy under an FDA Risk Evaluation and Mitigation Strategy program [188]. Alosetron is effective at relieving pain and reducing stool frequency and rectal urgency in women with IBS-D [3].

The 5-HT3RA ramosetron has also been studied as IBS-D therapy but has not received FDA approval. Ramosetron reduces defecation induced by corticotropin-releasing hormone and inhibited colonic nociception in preclinical studies. In randomized controlled trials of patients with IBS-D, ramosetron increased patient rates of global IBS symptom relief. In trials limited to male patients with IBS-D, ramosetron was as effective as mebeverine (an agent approved outside the United States) in improving stool consistency, relieving abdominal pain/discomfort, and improving health-related quality of life. Ramosetron shows a lower incidence of constipation versus other 5-HT3RAs and has not been associated with ischemic colitis [187]. In data stratified by sex, women reported significant relief of IBS symptoms only after two months, while men reported significant relief of IBS symptoms at all time points. Reasons for these differences are unknown [21].

The much less potent 5-HT3RA ondansetron (4 mg/day, range 2–6 mg/day) has also been found highly effective at improving stool consistency, reducing stool frequency, and reducing urgency. In one study, 70% with ondansetron (versus 16% with placebo) reported adequate IBS-D symptom relief. Worth noting is that ondansetron has been used for more than two decades without reports of ischemic colitis and has an excellent safety record; these features are important for IBS therapy selection [87].

Eluxadoline

Eluxadoline was approved in 2015 for IBS-D treatment in adults. This drug has therapeutic activity as a mixed mu-opioid receptor agonist and delta-opioid receptor antagonist, a novel mechanism of action developed to control GI function and decrease GI pain while mitigating the constipating effects of unopposed mu receptor agonist activity [21; 87].

FDA approval of eluxadoline was based on two multi-center, multi-national randomized controlled trials with 2,426 patients with IBS-D receiving twice-daily eluxadoline (75 mg or 100 mg) or placebo for 26 weeks. Therapeutic response was defined as concurrent improvement in diarrhea (using the BSFS) and abdominal pain. In both trials, the proportion of patients with reduced abdominal pain and improved stool consistency was significantly higher with eluxadoline than placebo, at both doses. Eluxadoline reduced IBS-D symptoms in men and women, and efficacy was sustained over six months with the 100-mg, twice daily dose. The most common adverse events were nausea (8%), constipation (8%), and abdominal pain (5.0%) [189; 190].

A small but definite risk (0.3%) of acute pancreatitis resulted from sphincter of Oddi spasm; all patients who developed this adverse effect had a history of cholecystectomy or significant ethanol consumption. According to the 2022 AGA guidelines, eluxadoline is contraindicated in patients without a gall bladder or those who drink more than three alcoholic beverages per day [218].

Mast Cell Stabilizers

In patients with IBS-D, jejunal mucosal biopsies have shown mast cell activation and hyperplasia, providing the theoretical basis for possible benefits with mast cell stabilizers [191]. Disodium cromoglycate and ketotifen act primarily by stabilizing the plasma membrane of mast cells and have been evaluated in the treatment of IBS-D [93].

In a six-month trial of disodium cromoglycate for IBS-D, jejunal biopsies showed reduced release of tryptase and reduced expression of toll-like receptor 2 and 4, and patients showed clinical improvement of bowel function [192]. In an earlier trial of patients with IBS-D with food intolerance, disodium cromoglycate (250 mg, four times per day) plus exclusion diet was associated with prolonged symptomatic benefit compared with exclusion diet alone [193; 194].

Ketotifen is a mast cell stabilizer with antihistamine properties that showed substantial improvement in patients with IBS despite no effect on mast cell parameters [195]. Further research suggests the effects mediated by histamine-blocking properties, and ketotifen may also be used in the treatment of abdominal pain-predominant IBS.

Muscarinic Type 3 Receptor Antagonists

Muscarinic type 3 (M3) receptor antagonists have beneficial effects in chronic diarrhea that include delayed small bowel and colonic transit, reduced rectal sensitivity, and reduced enterocyte secretion [93]. Preliminary evidence suggests greatest benefit with otilonium in IBS-D, with benefits shown in increased sensory thresholds to colonic volume and pressure, and reduction in abdominal pain [93; 196]. Otilonium is investigational in the United States.

Glutamine

Patients with IBS-D have increased gut permeability, and symptomatic patients with IBS have decreased intestinal glutamine synthetase levels. In a preliminary report of a placebo-controlled trial of 10 g glutamine three times per day in 61 patients, the glutamine arm was associated with improved abdominal pain, bloating, and diarrhea and restored intestinal permeability [93; 197].

Summary

During clinical development, rifaximin and eluxadoline demonstrated significant improvement in IBS-D endpoints versus placebo. In the absence of comparative randomized controlled trials, direct comparisons of alosetron, rifaximin, and eluxadoline efficacy cannot be made, but general efficacy estimates suggest similar and responses using outcome measures

of adequate relief and combined improvements in abdominal pain/stool form. Clinical use of these agents is suggested to follow a sequential scheme that considers patient symptoms and severity, prior medical history, mode of action, cost, availability, managed care coverage, and adverse event profiles [198]. The AGA guideline on the pharmacologic management of IBS-D recommends that selection of medication should be individualized, taking into account the dominant clinical features and individual patient's needs and preferences. A decision tool is offered based on a tiered approach, as follows [218]:

- First-line (mild): For diarrhea, loperamide and/or bile acid sequestrant; for abdominal pain, an antispasmodic (e.g., hyocyamine, peppermint oil)
- Second-line (moderate): Rifaximin, low-dose tricyclic antidepressant, or eluxadoline
- Third-line (refractory): Consider alosetron for women with severe abdominal pain, frequent bowel urgency or fecal incontinence, and/or disability/restriction of daily activities)

If abdominal pain persists and/or psychological symptoms supervene, the AGA recommends adding (or switching) to low-dose TCA or SNRI and/or brain-gut behavior therapies (e.g., CBT, hypnosis) [218].

CONSTIPATION-PREDOMINANT IBS

Constipation is one of the most common functional bowel disorder symptoms encountered in primary care and specialty practices. IBS with predominant constipation (IBS-C) is a subtype of IBS that accounts for more than one-third of IBS cases [215]. According to an IBS in America survey conducted by the AGA, persons with IBS-C are more likely to report feeling self-conscious, avoiding sex, having difficulty concentrating, and feeling unable to reach life's full potential [219]. IBS-C and other disorders of chronic constipation are associated with significant medical costs and a negative impact on quality of life [199].

In 2022, the AGA reviewed pharmacologic therapy and published updated guidelines for treatment of IBS-C [219].

Laxatives

Osmotic laxatives contain nonabsorbable ions or molecules that retain water in the bowel lumen. Polyethylene glycol (PEG), lactulose, and magnesium salts are most commonly used. Osmotic laxatives are generally useful to treat constipation but can promote or worsen abdominal pain and distension in IBS and are not recommended [44].

Stimulant laxatives promote water and electrolyte secretion in the colon or induce colonic peristalsis. They include diphenylmethanes (phenolphthalein, bisacodyl, sodium picosulfate) and anthraquinones (*Senna*, bearberry, *Aloe vera*). While useful for constipation, they can worsen abdominal pain and distension in patients with IBS [44]. In patients with IBS-C, a randomized controlled trial of PEG vs. placebo found stool frequency, stool consistency, and straining were improved, but abdominal pain and bloating were unimproved during the four-week study [142].

Secretagogues

Secretagogues act through different pharmacologic mechanisms to stimulate chloride release into the intestinal lumen, which stimulates intestinal fluid secretion to counteract constipation symptoms in IBS-C [200]. The most commonly used agents are lubiprostone and linaclotide.

Lubiprostone

Lubiprostone is a prostaglandin-derived fatty acid that activates intraluminal chloride channels and chloride ion secretion. This leads to a passive influx of water and sodium, which increases intestinal peristalsis and colonic laxation and decreases intestinal stool transit time. Lubiprostone does not affect pain thresholds during rectal distension [5; 87].

In patients with IBS-C, lubiprostone has proven effective in reducing constipation symptoms, but reduction of abdominal pain is much more modest (7% greater than placebo) and generally develops after one month of therapy. Side effects mostly involve mild-to-moderate nausea and diarrhea, and lubiprostone should be taken with food to limit dose-dependent nausea [3; 5].

Lubiprostone is approved for the treatment of chronic constipation and opioid-induced constipation for men and women at 24 mcg twice daily, and for IBS-C in women at 8 mcg twice daily. No dosage adjustment is required in patients with impaired renal function [44]. Additional research may expand its clinical use [87; 199].

Linaclotide

Linaclotide binds and activates guanylate cyclase C (GC-C) receptors expressed locally on the luminal surface of intestinal epithelium. GC-C receptor activation increases cyclic guanosine monophosphate concentrations, which activates the cystic fibrosis transmembrane conductance regulator to stimulate secretion of chloride and bicarbonate into the intestinal lumen. This leads to increased intestinal fluid and accelerated stool transit [87; 189].

In patients with IBS-C, randomized controlled trials have shown highly similar results across studies. Improvements in constipation, abdominal pain, discomfort or bloating, and stool consistency were 15% to 30% greater compared with placebo. These benefits persisted for 26 weeks. Diarrhea was the most commonly reported adverse event, occurring in 16.3% of patients receiving linaclotide, compared with 2.3% of patients receiving placebo. Efficacy and safety were similar in elderly and middle-aged adults [44; 87; 186]. Patients should take linaclotide (290 mcg) 30 to 60 minutes before breakfast to minimize the chance of diarrhea [5]. In consideration of additional evidence, the AGA 2022 guidelines make a strong recommendation for the use of linaclotide, noting that a network meta-analysis ranked this agent first in efficacy among secretagogues for IBS-C [219].

The AGA recommends using linaclotide (over no drug treatment) in patients with IBS-C.

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Strength of Recommendation/Level of Evidence: Strong recommendation/high-quality evidence

While lubiprostone and linaclotide led to improvements in stool frequency, constipation severity, and abdominal pain/discomfort in IBS-C, higher costs and adverse effects generally limit these agents to second-line therapy in IBS-C [201].

Plecanatide

Plecanatide is a nonabsorbed 16-amino acid peptide that, like linaclotide, stimulates GC-C receptors on intestinal epithelium, and via the same mediators causes secretion of fluid and electrolytes into the lumen of the bowel. Plecanatide is FDA-approved for treatment of IBS-C and chronic idiopathic constipation at a dosage of 3 mg once daily [219].

In two large phase 3 clinical trials of 12 weeks' duration, a total of 1,632 patients with IBS-C were randomized to treatment with plecanatide (814 patients) or placebo (818 patients). Patients treated with plecanatide showed greater IBS-C symptom relief (27.4%) than those receiving placebo (16.9%), as measured by meeting a predetermined responder end point for IBS-C [219]. Plecanatide demonstrated a higher success rate compared with placebo for improvement in abdominal pain, stool frequency, bloating, straining, and global measures of treatment satisfaction. Diarrhea was the most common side effect, reported by 4.3% of patients receiving plecanatide compared with 1.2% of those receiving placebo.

Tenapanor

Tenapanor is a first-in-class, small-molecule inhibitor of the intestinal sodium/hydrogen exchange isoform 3, which is expressed on the surface of the small bowel and colon and is responsible for the absorption of sodium. Tenapanor decreases absorption of sodium and phosphate and increases secretion of water into the intestinal lumen. This agent is FDA-approved for treatment of IBS-C at a dosage of 50 mg twice daily [219].

In three randomized controlled trials of 12 weeks' duration (688 patients in the treatment group and 684 in the placebo group), a greater proportion of patients with IBS-C taking tenapanor (58.1%) reported adequate relief of IBS symptoms compared with placebo (41.1%) [219]. Tenapanor demonstrated a higher success rate compared with placebo for improvement in abdominal pain. Diarrhea was the most common side effect, resulting in discontinuation of medication in 6.6% of patients in the tenapanor group compared with 1.1% in the placebo group.

5-HT4 Receptor Agonists

5-HT4 receptors are expressed on enteric neurons and in cardiac tissue. 5-HT4 receptor agonists (5-HT4RAs) facilitate fast excitatory cholinergic synaptic transmission between enteric neurons, which stimulates GI motility and increases fluid in the gastrointestinal tract. [93]. Tegaserod is the only FDA-approved 5-HT4 receptor agonist for the treatment of IBS; because of early trial cardiovascular adverse events in men and older women, this agent is only approved for use in adult women younger than 65 years of age with IBS-C [219; 220]. It is contraindicated in patients with more than one cardiovascular risk factor.

Prucalopride, mosapride, and three other 5-HT4RAs (velusetrag, naronapride, and YKP10811) are in development for IBS-C treatment. These drugs have greater cardiovascular safety compared with older 5-HT4RAs due to higher specificity at intestinal 5-HT4 receptors and low intrinsic activity in cardiac muscle. These agents are expected to show efficacy in IBS-C, but this awaits confirmation by large randomized controlled trials [93].

The 2022 AGA guideline on the pharmacologic management of IBS-C recommends that selection of medication be individualized, taking into account the dominant clinical features and individual patient's own needs and preferences. A decision tool is offered based on a tiered approach [219]:

- First-line (mild): For constipation, osmotic laxatives (e.g., PEG); for abdominal pain, antispasmotics (e.g., hyoscyamine, peppermint oil)
- Second-line (moderate): Secretagogues (linaclotide, lubiprostone, placanatide, tenapanor)
- Third-line: 5-HT4 receptor antagonist (tegaserod)

If abdominal pain persists and/or psychological symptoms supervene, the AGA recommends adding (or switching) to low dose TCA or SNRI and/or brain-gut behavior therapies (e.g., CBT, hypnosis) [219].

ABDOMINAL PAIN-PREDOMINANT IBS

Antispasmodics (Spasmolytics)

Abnormal contraction of smooth muscle within the colon and the GI tract underlies pain and other IBS symptoms in some patients, providing the rationale for using agents that relax smooth muscle [21]. Spasmolytics fall into three groups based on mechanism of action [44; 202]:

- Calcium channel blockers (e.g., alverine, otilonium, pinaverium bromide)
- Direct smooth muscle relaxants (e.g., mebeverine)
- Antimuscarinic/anticholinergic agents (e.g., hyoscine, cimetropium bromide, dicyclomine hydrochloride)

A review of 23 randomized controlled trials using various antispasmodics found that these agents improved IBS symptoms to a greater extent than placebo, but efficacy of individual antispasmodics varied. Only otilonium (investigational), hyoscine bromide, cimetropium bromide, pinaverium bromide, and dicyclomine showed significant improvements beyond placebo [196; 203].

Antispasmodic drugs with anticholinergic or calcium-channel blocking mechanisms are used for relieving diarrheal symptoms, abdominal pain and distension, and spasms in all IBS subtypes. However, anticholinergic agents may be better tolerated in patients with IBS-D [5; 183]. Otilonium and hyoscine have the best evidence of efficacy, and otilonium bromide is the most effective agent in preventing IBS symptom recurrence. Some patients with IBS have an exaggerated gastrocolic reflex that is in part cholinergic-mediated, and spasmolytics may be best suited for postprandial abdominal cramping and loose stools in these patients [5].

The most commonly reported adverse effects associated with spasmolytics include dry mouth, dizziness, and blurred vision; serious adverse events are rare. Spasmolytics with greater anticholinergic activity are more likely to induce blurred vision, urinary retention, constipation, and dry mouth. Anticholinergics should be avoided in the elderly and in patients with a history of acute myocardial infarction or hypertension. Use during pregnancy and breastfeeding is not recommended [5; 44].

Peppermint Oil

Peppermint oil possesses a calcium-channel blocking mechanism and is classified as an antispasmodic [5]. The spasmolytic properties of peppermint oil may modulate pain by attenuating visceral hypersensitivity [44]. Two systematic reviews found peppermint oil superior to placebo in the management of IBS pain [203; 204]. A 2014 review evaluated five trials enrolling a total of 482 patients and showed a statistically significant positive effect of peppermint oil over placebo [203].

Although peppermint oil is typically well tolerated, with no significant side effects reported with standard doses (250–750 mg two to three times/day), some patients may experience reflux symptoms, and allergic reactions, heartburn, and headache have been described [5]. Peppermint oil is available over the counter, and enteric-coated capsules are preferred [44].

Linaclotide

Linaclotide (290 mcg daily) demonstrated improvement in abdominal pain in two large, phase 3 studies in IBS-C, with one trial extending treatment out to 26 weeks [93].

Antidepressants

As discussed, antidepressants are commonly used to treat pain symptoms associated with chronic functional GI disorders, including IBS. In a Cochrane review, the TCAs desipramine (25–100 mg at bedtime) and amitriptyline (10–50 mg at bedtime) demonstrated some global improvements of abdominal pain [93].

Pregabalin

Pregabalin, an a2d ligand that inhibits release of a number of excitatory neurotransmitters, may alleviate visceral pain in patients with IBS [106; 205]. Pregabalin increases distension sensory thresholds to normal levels in patients with IBS with rectal hypersensitivity. Studies are in progress to evaluate efficacy in centrally mediated abdominal pain syndrome (formerly termed functional abdominal pain syndrome) [93].

Histamine H1 Receptor Antagonists

Ketotifen

Ketotifen is a mast cell stabilizer with antihistamine properties. An eight-week randomized controlled trial showed evidence of improved pain, bloating, flatulence, diarrhea, quality of life, sleep, and sexual functioning in patients with IBS-D, despite lack of reduction in mast cell mediators [195]. The underlying mechanism of action was identified as histamine H1 receptor antagonism, which helped prompt further study of H1 receptor antagonists in patients with IBS [206].

Ebastine

Evidence suggests disordered GI motility, psychosocial distress, and visceral hypersensitivity converge on common pathways, including transient receptor potential cation channel subfamily V (TRPV). TRPV expressed on sensory neurons throughout the gut produces pain when activated by inflammatory mediators [207].

Researchers examined colorectal biopsies of patients with IBS and found greater TRPV-4 metabolite levels, which correlated with abdominal pain and bloating severity, and significantly greater nervous tissue and nerve growth mediators [207]. From these discoveries and results of ketotifen in the treatment of IBS, the histamine H1 receptor antagonist ebastine was studied for possible effects on visceral pain and hypersensitivity in 56 patients with IBS, randomized to ebastine (20 mg/day) or placebo. Over 12 weeks, a significant reduction of abdominal pain was found with ebastine compared to placebo and to baseline. Significantly more patients treated with ebastine (vs. placebo) had at least considerable relief of symptoms (46% vs. 12%) and lower mean abdominal pain scores (0–100 scale: ebastine 38, placebo 62). Quality of life was significantly improved on all IBS-QOL subscales in the ebastine group compared with baseline and placebo [206; 207].

Hypersensitive and normosensitive subgroups did not differ in ebastine response. Visceral pain response, as measured by rectal distension, had no association with clinical response, showing barostat findings as an invalid outcome measure. Most importantly, this study suggests H1-receptor blockade may represent an effective treatment for IBS abdominal pain regardless of subtype. This is encouraging given the lack of targeted treatments for visceral hypersensitivity and abdominal pain in IBS [206; 207].

Fecal Microbial Transplantation

Fecal microbiota transplants have been used in the last decade for severe cases of *Clostridioides difficile* infection, with success rates greater than 90%. Fecal microbiota transplants may be a therapeutic option for severe refractory IBS or inflammatory bowel disease, but current FDA regulations limit use to the treatment of severe *C. difficile* infection [208].

In a randomized, double-blind placebo-controlled trial involving 52 adult patients with moderate-to-severe IBS, fecal microbiota transplantation successfully altered gut flora in patients with IBS, but patients in the placebo group experienced greater symptom relief after three months than did patients in the treatment group [211]. The authors concluded that altering gut microbiota is not an effective means of obtaining symptom improvement in patients with IBS. A 2019 literature review and meta-analysis, conducted to evaluate the combined outcome of improvement in global IBS syndrome, found no significant difference at 12 weeks in fecal microbiota transplantation versus placebo [212].

Concerns over introducing pathologic organisms must be addressed before fecal microbiota transplant is approved in clinical management of inflammatory bowel disease. An example is the case of a female patient with *C. difficile* infection who received fecal microbiota transplant from an obese person and subsequently became obese herself [208].

SPECIALIST REFERRAL

Specialist referral from primary care should be considered for patients with IBS who do not respond or are intolerant to management with dietary and lifestyle changes, common laxatives, spasmolytics, or antidepressants [44]. Referral is also indicated if defecation dysfunction is suspected, there is unexplained worsening in clinical status, or there is an unambiguous need for a second expert opinion.

CONSIDERATIONS FOR NON-ENGLISH-PROFICIENT PATIENTS

As a result of the evolving racial and immigration demographics in the United States, interaction with patients for whom English is not a native language is inevitable. Because patient education is such an important aspect of the care of patients with IBS, it is each practitioner's responsibility to ensure that information and instructions are explained in such a way that allows for patient or caregiver understanding. When there is an obvious disconnect in the communication process between the practitioner and patient due to the patient's lack of proficiency in the English language, an interpreter is required. (In many cases, the terms "interpreting" and "translating" are used interchangeably, but interpreting is specifically associated with oral communication while translating refers to written text.) Frequently, this may be easier said than done, as there may be institutional and/or patient barriers.

Depending upon the patient's language, an interpreter may be difficult to locate. Or, an organization may not have the funds to bring in an interpreter. Also, bringing in an interpreter creates a triangular relationship with a host of communication dynamics that must be negotiated. Many view interpreters merely as neutral individuals who communicate information back and forth. However, another perspective is that the interpreter is an active agent, negotiating between two cultures and assisting in promoting culturally competent communication and practice. In this more active role, the interpreter's behavior is also influenced by a host of cultural variables such as gender, class, religion, educational differences, and power/authority perceptions of the patient. Consequently, an intricate, triangular relationship develops between all three parties. Another factor affecting the communication process is the fact that many interpreters are not adequately trained in the art of interpretation in mental health and general health settings, as there are many technical and unfamiliar terms. An ideal interpreter goes beyond being merely proficient in the needed language/dialect. Interpreters who are professionally trained have covered aspects of ethics, impartiality, accuracy, and completeness. They are also well-versed in interpreting both the overt and latent content of information without changing any meanings and without interjecting their own biases and opinions. Furthermore, knowledge about cross-cultural communication and all the subtle nuances of the dynamics of communicating in a mental health or general health setting is vital.

On the patients' side, they may be wary about utilizing interpreters for a host of reasons. They may find it difficult to express themselves through an interpreter. If an interpreter is from the same community as the patient, the patient may have concerns about sharing private information with an individual who is known in the community and the extent to which the information disclosed would remain confidential. In some cases, raising the issue of obtaining an interpreter causes the patient to feel insulted that their language proficiency has been questioned. Finally, if an interpreter is from a conflicting ethnic group, the patient may refuse having interpreter services. The ideal situation is to have a well-trained interpreter who is familiar with health and mental health concepts.

If an interpreter is required, the practitioner must acknowledge that an interpreter is more than a body serving as a vehicle to transmit information verbatim from one party to another. Instead, the interpreter should be regarded as part of a collaborative team, bringing to the table a specific set of skills and expertise. Several important guidelines should be adhered to in order to foster a beneficial working relationship and a positive atmosphere.

A briefing time between the practitioner and interpreter held prior to the meeting with the patient is crucial. The interpreter should understand the goal of the session, issues that will be discussed, specific terminology that may be used to allow for advance preparation, preferred translation formats, and sensitive topics that might arise. It is important for the patient, interpreter, and practitioner to be seated in such a way that the practitioner can see both the interpreter and patient. Some experts recommend that the interpreter sit next to the patient, both parties facing the practitioner.

The practitioner should always address the patient directly. For example, the practitioner should query the patient, "How do you feel?" versus asking the interpreter, "How does she feel?" The practitioner should also always refer to the patient as "Mr./Mrs. D" rather than "he" or "she." This avoids objectifying the patient.

At the start of the session, the practitioner should clearly identify his/her role and the interpreter's role. This will prevent the patient from developing a primary relationship or alliance with the interpreter, turning to the interpreter as the one who sets the intervention. The practitioner should also be attuned to the age, gender, class, and/or ethnic differences between the patient and the interpreter. For example, if the patient is an older Asian male immigrant and the interpreter is a young Asian woman, the practitioner should be sensitive to whether the patient is uncomfortable given the fact he may be

more accustomed to patriarchal authority structures. At the conclusion of the session, it is advisable to have a debriefing time between the practitioner and the interpreter to review the session.

In this multicultural landscape, interpreters are a valuable resource to help bridge the communication and cultural gap between patients and practitioners. Interpreters are more than passive agents who translate and transmit information back and forth from party to party. When they are enlisted and treated as part of the interdisciplinary clinical team, they serve as cultural brokers, who ultimately enhance the clinical encounter. In any case in which information regarding diagnostic procedures, treatment options and medication/treatment measures are being provided, the use of an interpreter should be considered.

CONCLUSION

IBS is common in the general population and has a significant medical and socioeconomic impact. Standard management of IBS has involved psychological support, dietary measures, and pharmacotherapy directed at symptoms. IBS has long been considered a notoriously difficult condition to manage, because the pathophysiology has been poorly understood. Advances in the understanding of the disease's etiology and pathophysiology are informing the use of novel treatment approaches. This course has reviewed current concepts of pathogenesis, diagnosis, and treatment to provide clinicians with the information necessary to appropriately diagnose and treat IBS and improve patients' quality of life.

RESOURCES

American College of Gastroenterology
https://gi.org

American Gastroenterological Association
https://gastro.org

International Foundation for Functional Gastrointestinal Disorders
https://iffgd.org
https://aboutibs.org

National Institute of Diabetes and Digestive and Kidney Diseases
https://www.niddk.nih.gov/health-information/digestive-diseases/irritable-bowel-syndrome

North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition
https://naspghan.org

The Rome Foundation
https://theromefoundation.org

Society of Gastroenterology Nurses and Associates
https://www.sgna.org

Implicit Bias in Health Care

The role of implicit biases on healthcare outcomes has become a concern, as there is some evidence that implicit biases contribute to health disparities, professionals' attitudes toward and interactions with patients, quality of care, diagnoses, and treatment decisions. This may produce differences in help-seeking, diagnoses, and ultimately treatments and interventions. Implicit biases may also unwittingly produce professional behaviors, attitudes, and interactions that reduce patients' trust and comfort with their provider, leading to earlier termination of visits and/or reduced adherence and follow-up. Disadvantaged groups are marginalized in the healthcare system and vulnerable on multiple levels; health professionals' implicit biases can further exacerbate these existing disadvantages.

Interventions or strategies designed to reduce implicit bias may be categorized as change-based or control-based. Change-based interventions focus on reducing or changing cognitive associations underlying implicit biases. These interventions might include challenging stereotypes. Conversely, control-based interventions involve reducing the effects of the implicit bias on the individual's behaviors. These strategies include increasing awareness of biased thoughts and responses. The two types of interventions are not mutually exclusive and may be used synergistically.

Works Cited

1. Pearson JS, Niven RM, Meng J, Atarodi S, Whorwell PJ. Immunoglobulin E in irritable bowel syndrome: another target for treatment? A case report and literature review. *Ther Adv Gastroenterol*. 2015;8(5):270-277.
2. Drossman DA. Functional gastrointestinal disorders: history, pathophysiology, clinical features, and Rome IV. *Gastroenterology*. 2016;150:1262-1279.
3. Lacy BE, Mearin F, Chang L, et al. Bowel disorders. *Gastroenterology*. 2016;150:1393-1407.
4. Canavan C, West J, Card T. The epidemiology of irritable bowel syndrome. *Clin Epidemiol*. 2014;6:71-80.
5. Chey WD, Kurlander J, Eswaran S. Irritable bowel syndrome: a clinical review. *JAMA*. 2015;313(9):949-958.
6. Lovell RM, Ford AC. Effect of gender on prevalence of irritable bowel syndrome in the community: systematic review and meta-analysis. *Am J Gastroenterol*. 2012;107(7):991-1000.
7. Freeman K, Cleveland Clinic Center for Continuing Education. Irritable Bowel Syndrome. Available at https://www.clevelandclinicmeded.com/online/casebased/decisionmaking/ibs/. Last accessed November 12, 2022.
8. Lee V, Guthrie E, Robinson A, et al. Functional bowel disorders in primary care: factors associated with health-related quality of life and doctor consultation. *J Psychosom Res*. 2008;64(2):129-138.
9. Sayuk GS, Wolf R, Chang L. Comparison of symptoms, healthcare utilization, and treatment in diagnosed and undiagnosed individuals with diarrhea-predominant irritable bowel syndrome. *Am J Gastroenterol*. 2017;112:692.
10. Koloski NA, Talley NJ, Huskic SS, Boyce PM. Predictors of conventional and alternative health care seeking for irritable bowel syndrome and functional dyspepsia. *Aliment Pharmacol Ther*. 2003;17(6):841-851.
11. Lovell RM, Ford AC. Global prevalence of and risk factors for irritable bowel syndrome: a meta-analysis. *Clin Gastroenterol Hepatol*. 2012;10(7):712-721.e4.
12. Fadgyas-Stanculete M, Buga AM, Popa-Wagner A, Dumitrascu DL. The relationship between irritable bowel syndrome and psychiatric disorders: from molecular changes to clinical manifestations. *J Mol Psychiatry*. 2014;2:4.
13. Halder SL, Locke GR III, Schleck CD, Zinsmeister AR, Melton LJ 3rd, Talley NJ. Natural history of functional gastrointestinal disorders: a 12-year longitudinal population-based study. *Gastroenterology*. 2007;133(3):799-807.
14. Riedl A, Schmidtmann M, Stengel A, et al. Somatic comorbidities of irritable bowel syndrome: a systematic analysis. *J Psychosom Res*. 2008;64(6):573-582.
15. Drossman DA, Hasler WL. Rome IV—functional GI disorders: disorders of gut-brain interaction. *Gastroenterology*. 2016;150(6):1257-1261.
16. Dancey CP, Hutton-Young SA, Moye S, Devins GM. Perceived stigma, illness intrusiveness and quality of life in men and women with irritable bowel syndrome. *Psychol Health Med*. 2002;7(4):381-395.
17. Jones MP, Keefer L, Bratten J, et al. Development and initial validation of a measure of perceived stigma in irritable bowel syndrome. *Psychol Health Med*. 2009;14(3):367-374.
18. Fond G, Loundou A, Hamdani N, et al. Anxiety and depression comorbidities in irritable bowel syndrome (IBS): a systematic review and meta-analysis. *Eur Arch Psychiatry Clin Neurosci*. 2014;264(8):651-660.
19. Rey de Castro NG, Miller V, Carruthers HR, Whorwell PJ. Irritable bowel syndrome: a comparison of subtypes. *J Gastroenterol Hepatol*. 2015;30(2):279-285.
20. Patel P, Bercik P, Morgan D, et al. Irritable bowel syndrome is significantly associated with somatisation in 840 patients, which may drive bloating. *Aliment Pharmacol Ther*. 2015;41(5):449-458.
21. Foxx-Orenstein AE. New and emerging therapies for the treatment of irritable bowel syndrome: an update for gastroenterologists. *Ther Adv Gastroenterol*. 2016;9(3):354-375.
22. Gulewitsch M, Enck P, Hautzinger M, Schlarb A. Irritable bowel syndrome symptoms among German students: prevalence, characteristics, and associations to somatic complaints, sleep, quality of life, and childhood abdominal pain. *Eur J Gastroenterol Hepatol*. 2011;23(4):311-316.
23. Singh P, Agnihotri A, Pathak M, et al. Psychiatric, somatic and other functional gastrointestinal disorders in patients with irritable bowel syndrome at a tertiary care center. *J Neurogastroenterol Motil*. 2012;18(3):324-331.
24. Walitt B, Ceko M, Gracely JL, Gracely RH. Neuroimaging of central sensitivity syndromes: key insights from the scientific literature. *Curr Rheumatol Rev*. 2016;12(1):55-87.
25. Hillilä MT, Siivola MT, Färkkilä MA. Comorbidity and use of health-care services among irritable bowel syndrome sufferers. *Scand J Gastroenterol*. 2007;42(7):799-806.
26. Whitehead WE, Palsson O, Jones KR. Systematic review of the comorbidity of irritable bowel syndrome with other disorders: what are the causes and implications? *Gastroenterology*. 2002;122(4):1140-1156.
27. Choung R, Locke GR III, Zinsmeister A, Schleck CD, Talley NJ. Psychosocial distress and somatic symptoms in community subjects with irritable bowel syndrome: a psychological component is the rule. *Am J Gastroenterol*. 2009;104(7):1772-1779.
28. Tang YR, Yang WW, Liang ML, Xu XY, Wang MF, Lin L. Age-related symptom and life quality changes in women with irritable bowel syndrome. *World J Gastroenterol*. 2012;18(48):7175-7183.

29. Aggarwal VR, McBeth J, Zakrzewska JM, Lunt M, Macfarlane GJ. The epidemiology of chronic syndromes that are frequently unexplained: do they have common associated factors? *Int J Epidemiol.* 2006;35(2):468-476.
30. Black TP, Manolakis CS, Di Palma JA. "Red flag" evaluation yield in irritable bowel syndrome. *J Gastrointestin Liver Dis.* 2012;21(2):153-156.
31. Porter CK, Cash BD, Pimentel M, Akinseye A, Riddle MS. Risk of inflammatory bowel disease following a diagnosis of irritable bowel syndrome. *BMC Gastroenterol.* 2012;12:55.
32. García Rodríguez LA, Ruigómez A, Wallander MA, Johansson S, Olbe L. Detection of colorectal tumor and inflammatory bowel disease during follow-up of patients with initial diagnosis of irritable bowel syndrome. *Scand J Gastroenterol.* 2000;35(3):306-311.
33. Williams RE, Black CL, Kim HY, et al. Determinants of healthcare-seeking behaviour among subjects with irritable bowel syndrome. *Aliment Pharmacol Ther.* 2006;23(11):1667-1675.
34. Mearin F, Baró E, Roset M, Badía X, Zárate N, Pérez I. Clinical patterns over time in irritable bowel syndrome: symptom instability and severity variability. *Am J Gastroenterol.* 2004;99(1):113-121.
35. Ford AC, Forman D, Bailey AG, Axon AT, Moayyedi P. Irritable bowel syndrome: a 10-yr natural history of symptoms and factors that influence consultation behavior. *Am J Gastroenterol.* 2008;103(5):1229-1239.
36. El-Serag HB, Pilgrim P, Schoenfeld P. Systemic review: natural history of irritable bowel syndrome. *Aliment Pharmacol Ther.* 2004;19(8):861-870.
37. Agréus L, Svärdsudd K, Talley NJ, Jones MP, Tibblin G. Natural history of gastroesophageal reflux disease and functional abdominal disorders: a population based study. *Am J Gastroenterol.* 2001;96(10):2905-2914.
38. Stanghellini V, Tosetti C, Barbara G, et al. Dyspeptic symptoms and gastric emptying in the irritable bowel syndrome. *Am J Gastroenterol.* 2002;97(11):2738-2743.
39. Levy RL, Jones KR, Whitehead WE, Feld SI, Talley NJ, Corey LA. Irritable bowel syndrome in twins: heredity and social learning both contribute to etiology. *Gastroenterology.* 2001;121(4):799-804.
40. Mohammed I, Cherkas LF, Riley SA, Spector TD, Trudgill NJ. Genetic influences in irritable bowel syndrome: a twin study. *Am J Gastroenterol.* 2005;100(6):1340-1344.
41. Vandvik PO, Wilhelmsen I, Ihlebaek C, Farup PG. Comorbidity of irritable bowel syndrome in general practice: a striking feature with clinical implications. *Aliment Pharmacol Ther.* 2004;20(10):1195-1203.
42. Engsbro AL, Simren M, Bytzer P. Short-term stability of subtypes in the irritable bowel syndrome: prospective evaluation using the Rome III classification. *Aliment Pharmacol Ther.* 2012;35(3):350-359.
43. Müller-Lissner SA, Kamm MA, Scarpignato C, Wald A. Myths and misconceptions about chronic constipation. *Am J Gastroenterol.* 2005;100(1):232-242.
44. Mearin F, Ciriza C, Mínguez M, et al. Clinical practice guideline: irritable bowel syndrome with constipation and functional constipation in the adult. *Rev Esp Enferm Dig.* 2016;108(6):332-363.
45. Drossman DA, Morris CB, Hu Y, et al. A prospective assessment of bowel habit in irritable bowel syndrome in women: defining an alternator. *Gastroenterology.* 2005;128(3):580-589.
46. Chang JY, Locke GR 3rd, McNally MA, et al. Impact of functional gastrointestinal disorders on survival in the community. *Am J Gastroenterol.* 2010;105(4):822-832.
47. Ballou S, Bedell A, Keefer L. Psychosocial impact of irritable bowel syndrome: a brief review. *World J Gastrointest Pathophysiol.* 2015;6(4):120-123.
48. Spiegel BM. The burden of IBS: looking at metrics. *Curr Gastroenterol Rep.* 2009;11(4):265-269.
49. Sethi S, Wadhwa V, LeClair J, et al. In-patient discharge rates for the irritable bowel syndrome: an analysis of national trends in the United States from 1997 to 2010. *Aliment Pharmacol Ther.* 2013;38(11-12):1338-1346.
50. Singh P, Staller K, Barshop K, et al. Patients with irritable bowel syndrome-diarrhea have lower disease-specific quality of life than irritable bowel syndrome-constipation. *World J Gastroenterol.* 2015;21(26):8103-8109.
51. Ringel Y, Williams R, Kalilani L, Cook S. Prevalence, characteristics, and impact of bloating symptoms in patients with irritable bowel syndrome. *Clin Gastroenterol Hepatol.* 2009;7(1):68-72.
52. Kanazawa M, Miwa H, Nakagawa A, Kosako M, Akiho H, Fukudo S. Abdominal bloating is the most bothersome symptom in irritable bowel syndrome with constipation (IBS-C): a large population-based Internet survey in Japan. *BioPsychoSoc Med.* 2016;10:19.
53. Stephenson JJ, Buono JL, Spalding WM, et al. Impact of irritable bowel syndrome with constipation on work productivity and daily activity among commercially insured patients in the United States. *Value Health.* 2014;17(7):A370.
54. Budtz-Lilly A, Schröder A, Rask MT, Fink P, Vestergaard M, Rosendal M. Bodily distress syndrome: a new diagnosis for functional disorders in primary care? *BMC Fam Pract.* 2015;16:180.
55. Van Oudenhove L, Levy RL, Crowell MD, et al. Biopsychosocial aspects of functional gastrointestinal disorders: how central and environmental processes contribute to the development and expression of functional gastrointestinal disorders. *Gastroenterology.* 2016;150(6):1355-1367.

56. Levy RL, Whitehead WE, Walker LS, et al. Increased somatic complaints and health-care utilization in children: effects of parent IBS status and parent response to gastrointestinal symptoms. *Am J Gastroenterol.* 2004;99(12):2442-2451.
57. Drossman DA. Redux: do little bellyachers grow up to become big bellyachers? *Clin Gastroenterol Hepatol.* 2014;12(12):2033-2036.
58. Levy RL, Langer S, Walker LS, et al. Twelve month follow-up of cognitive behavioral therapy for children with functional abdominal pain. *JAMA Pediatr.* 2013;167(2):178-184.
59. Langer SL, Romano JM, Levy RL, Walker LS, Whitehead WE. Catastrophizing and parental response to child symptom complaints. *Child Health Care.* 2009;38(3):169-184.
60. Nemeroff CB. Paradise lost: the neurobiological and clinical consequences of child abuse and neglect. *Neuron.* 2016;89(5):892-909.
61. Bradford K, Shih W, Videlock EJ, et al. Association between early adverse life events and irritable bowel syndrome. *Clin Gastroenterol Hepatol.* 2012;10(4):385-390.
62. Drossman DA. Abuse, trauma, and GI illness: is there a link? *Am J Gastroenterol.* 2011;106(1):14-25.
63. Murray CD, Flynn J, Ratcliffe L, Jacyna MR, Kamm MA, Emmanuel AV. Effect of acute physical and psychological stress on gut autonomic innervation in irritable bowel syndrome. *Gastroenterology.* 2004;127(6):1695-1703.
64. Bennett EJ, Tennant CC, Piesse C, Badcock CA, Kellow JE. Level of chronic life stress predicts clinical outcome in irritable bowel syndrome. *Gut.* 1998;43(2):256-261.
65. Lackner JM, Gudleski GD, Firth R, et al. Negative aspects of close relationships are more strongly associated than supportive personal relationships with illness burden of irritable bowel syndrome. *J Psychosom Res.* 2013;74(6):493-500.
66. Lackner JM, Brasel AM, Quigley BM, et al. The ties that bind: perceived social support, stress, and IBS in severely affected patients. *Neurogastroenterol Motil.* 2010;22(8):893-900.
67. Addolorato G, Mirijello A, D'Angelo C, et al. State and trait anxiety and depression in patients affected by gastrointestinal diseases: psychometric evaluation of 1641 patients referred to an internal medicine outpatient setting. *Int J Clin Pract.* 2008;62(7):1063-1069.
68. Bouchoucha M, Hejnar M, Devroede G, Babba T, Bon C, Benamouzig R. Anxiety and depression as markers of multiplicity of sites of functional gastrointestinal disorders: a gender issue? *Clin Res Hepatol Gastroenterol.* 2013;37(4):422-430.
69. Miller V, Hopkins L, Whorwell PJ. Suicidal ideation in patients with irritable bowel syndrome. *Clin Gastroenterol Hepatol.* 2004;2(12):1064-1068.
70. Van Oudenhove L, Vandenberghe J, Vos R, Holvoet L, Tack J. Factors associated with co-morbid irritable bowel syndrome and chronic fatigue-like symptoms in functional dyspepsia. *Neurogastroenterol Motil.* 2011;23(6):524-e202.
71. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders.* 5th ed. Washington, DC: American Psychiatric Association; 2013.
72. Dimsdale JE, Creed F, Escobar J, et al. Somatic symptom disorder: an important change in DSM. *J Psychosom Res.* 2013;75(3):223-228.
73. Duddu V, Isaac MK, Chaturvedi SK. Somatization, somatosensory amplification, attribution styles and illness behaviour: a review. *Int Rev Psychiatry.* 2006;18(1):25-33.
74. Agosti V, Quitkin FM, Stewart JW, McGrath PJ. Somatization as a predictor of medication discontinuation due to adverse events. *Int Clin Psychopharmacol.* 2002;17(6):311-314.
75. Van Oudenhove L, Vandenberghe J, Vos R, Fischler B, Demyttenaere K, Tack J. Abuse history, depression, and somatization are associated with gastric sensitivity and gastric emptying in functional dyspepsia. *Psychosom Med.* 2011;73(8):648-655.
76. Lackner JM, Ma CX, Keefer L, et al. Type, rather than number, of mental and physical comorbidities increases the severity of symptoms in patients with irritable bowel syndrome. *Clin Gastroenterol Hepatol.* 2013;11(9):1147-1157.
77. Whitehead WE, Palsson OS, Levy RR, Feld AD, Turner M, Von Korff M. Comorbidity in irritable bowel syndrome. *Am J Gastroenterol.* 2007;102(12):2767-2776.
78. Chilcot J, Moss-Morris R. Changes in illness-related cognitions rather than distress mediate improvements in irritable bowel syndrome (IBS) symptoms and disability following a brief cognitive behavioural therapy intervention. *Behav Res Ther.* 2013;51(10):690-695.
79. Yeo A, Boyd P, Lumsden S, et al. Association between a functional polymorphism in the serotonin transporter gene and diarrhoea predominant irritable bowel syndrome in women. *Gut.* 2004;53(10):1452-1458.
80. Fukudo S, Kaneko H, Akiho H, et al. Evidence-based clinical practice guidelines for irritable bowel syndrome. *J Gastroenterol.* 2015;50(1):11-30.
81. Padhy SK, Sahoo S, Mahajan S, Sinha SK. Irritable bowel syndrome: is it "irritable brain" or "irritable bowel"? *J Neurosci Rural Pract.* 2015;6(4):568-577.
82. Spiller R, Garsed K. Postinfectious irritable bowel syndrome. *Gastroenterology.* 2009;136(6):1979-1988.
83. Cremon C, Stanghellini V, Pallotti F, et al. *Salmonella* gastroenteritis during childhood is a risk factor for irritable bowel syndrome in adulthood. *Gastroenterology.* 2014;147(1):69-77.
84. Malagelada JR, Malagelada C. Mechanism-oriented therapy of irritable bowel syndrome. *Adv Ther.* 2016;33(6):877-893.
85. Spiller R, Lam C. An update on post-infectious irritable bowel syndrome: role of genetics, immune activation, serotonin and altered microbiome. *J Neurogastroenterol Motil.* 2012;18(3):258-268.

86. Jalanka-Tuovinen J, Salojarvi J, Salonen A, et al. Faecal microbiota composition and host-microbe cross-talk following gastroenteritis and in postinfectious irritable bowel syndrome. *Gut*. 2014;63(11):1737-1745.
87. Spiller R. Irritable bowel syndrome: new insights into symptom mechanisms and advances in treatment. *F1000Res*. 2016;5:780.
88. McCarville JL, Caminero A, Verdu EF. Novel perspectives on therapeutic modulation of the gut microbiota. *Ther Adv Gastroenterol*. 2016;9(4):580-593.
89. Kassinen A, Krogius-Kurikka L, Makivuokko H, et al. The fecal microbiota of irritable bowel syndrome patients differs significantly from that of healthy subjects. *Gastroenterology*. 2007;133(1):24-33.
90. Cryan JF, Dinan TG. Mind-altering microorganisms: the impact of the gut microbiota on brain and behaviour. *Nat Rev Neurosci*. 2012;13(10):701-712.
91. Tana C, Umesaki Y, Imaoka A, Handa T, Kanazawa M, Fukudo S. Altered profiles of intestinal microbiota and organic acids may be the origin of symptoms in irritable bowel syndrome. *Neurogastroenterol Motil*. 2010;22(5):512-519.
92. Wedlake L, A'Hern R, Russell D, Thomas K, Walters JR, Andreyev HJ. Systematic review: the prevalence of idiopathic bile acid malabsorption as diagnosed by SeHCAT scanning in patients with diarrhoea-predominant irritable bowel syndrome. *Aliment Pharmacol Ther*. 2009;30(7):707-717.
93. Camilleri M, Buéno L, Andresen V, De Ponti F, Choi MG, Lembo A. Pharmacological, pharmacokinetic, and pharmacogenomic aspects of functional gastrointestinal disorders. *Gastroenterology*. 2016;150:1319-1331.
94. Hayes PA, Fraher MH, Quigley EM. Irritable bowel syndrome: the role of food in pathogenesis and management. *Gastroenterol Hepatol (N Y)*. 2014;10(3):164-174.
95. Rajilić-Stojanović M, Jonkers DM, Salonen P, et al. Intestinal microbiota and diet in IBS: causes, consequences, or epiphenomena? *Am J Gastroenterol*. 2015;110(2):278-287.
96. Camilleri M. Peripheral mechanisms in irritable bowel syndrome. *N Engl J Med*. 2012;367(17):1626-1635.
97. Biesiekierski JR, Newnham ED, Irving PM, et al. Gluten causes gastrointestinal symptoms in subjects without celiac disease: a double-blind randomized placebo-controlled trial. *Am J Gastroenterol*. 2011;106(3):508-514.
98. Vazquez-Roque MI, Camilleri M, Smyrk T, et al. A controlled trial of gluten-free diet in patients with irritable bowel syndrome-diarrhea: effects on bowel frequency and intestinal function. *Gastroenterology*. 2013;144(5):903-911.
99. Carroccio A, Mansueto P, Iacono G, et al. Non-celiac wheat sensitivity diagnosed by double-blind placebo-controlled challenge: exploring a new clinical entity. *Am J Gastroenterol*. 2012;107(12):1898-1906.
100. Mayer EA, Tillisch K. The brain-gut axis in abdominal pain syndromes. *Annu Rev Med*. 2011;62:381-396.
101. Dorn SD, Palsson OS, Thiwan SIM, et al. Increased colonic pain sensitivity in irritable bowel syndrome is the result of an increased tendency to report pain rather than increased neurosensory sensitivity. *Gut*. 2007;56(9):1202-1209.
102. Dickhaus B, Mayer EA, Firooz N, et al. Irritable bowel syndrome patients show enhanced modulation of visceral perception by auditory stress. *Am J Gastroenterol*. 2003;98(1):135-143.
103. Elsenbruch S, Rosenberger C, Enck P, Forsting M, Schedlowski M, Gizewski ER. Affective disturbances modulate the neural processing of visceral pain stimuli in irritable bowel syndrome: an fMRI study. *Gut*. 2010;59:489-495.
104. Van Oudenhove L, Aziz Q. The role of psychosocial factors and psychiatric disorders in functional dyspepsia. *Nat Rev Gastroenterol Hepatol*. 2013;10(3):158-167.
105. Chakiath RJ, Siddall PJ, Kellow JE, et al. Descending pain modulation in irritable bowel syndrome (IBS): a systematic review and meta-analysis. *Syst Rev*. 2015;4:175.
106. Keefer L, Drossman DA, Guthrie E, et al. Centrally mediated disorders of gastrointestinal pain. *Gastroenterology*. 2016;150:1408-1419.
107. Tillisch K, Mayer EA, Labus JS. Quantitative meta-analysis identifies brain regions activated during rectal distension in irritable bowel syndrome. *Gastroenterology*. 2011;140(1):91-100.
108. Aizawa E, Sato Y, Kochiyama T, et al. Altered cognitive function of prefrontal cortex during error feedback in patients with irritable bowel syndrome, based on fMRI and dynamic causal modeling. *Gastroenterology*. 2012;143(5):1188-1198.
109. Van Oudenhove L, Labus J, Dupont P, et al. Altered brain network connectivity associated with increased perceptual response to aversive gastric distension and its expectation in functional dyspepsia. *Neurogastroenterol Motil*. 2010;22:20-21.
110. Jiang Z, Dinov ID, Labus J, et al. Sex-related differences of cortical thickness in patients with chronic abdominal pain. *PLoS One*. 2013;8(9):e73932.
111. Labus JS, Dinov ID, Jiang Z, et al. Irritable bowel syndrome in female patients is associated with alterations in structural brain networks. *Pain*. 2014;155(1):137-149.
112. Seminowicz DA, Labus JS, Bueller JA, et al. Regional gray matter density changes in brains of patients with irritable bowel syndrome. *Gastroenterology*. 2010;139(1):48-57.
113. Blankstein U, Chen J, Diamant NE, Davis KD. Altered brain structure in irritable bowel syndrome: potential contributions of pre-existing and disease-driven factors. *Gastroenterology*. 2010;138(5):1783-1789.
114. Zeng F, Qin W, Yang Y, et al. Regional brain structural abnormality in meal-related functional dyspepsia patients: a voxel-based morphometry study. *PLoS One*. 2013;8(7):e68383.

115. Ellingson BM, Mayer E, Harris RJ, et al. Diffusion tensor imaging detects microstructural reorganization in the brain associated with chronic irritable bowel syndrome. *Pain*. 2013;154(9):1528-1541.

116. Chen JY, Blankstein U, Diamant NE, Davis KD. White matter abnormalities in irritable bowel syndrome and relation to individual factors. *Brain Res*. 2011;1392:121-131.

117. Zhou G, Qin W, Zeng F, et al. White-matter microstructural changes in functional dyspepsia: a diffusion tensor imagine study. *Am J Gastroenterol*. 2013;108(2):260-269.

118. Lehrer JK, Lichtenstein GR. Irritable Bowel Syndrome. Available at https://emedicine.medscape.com/article/180389-overview. Last accessed November 12, 2022.

119. Bharadwaj S, Barber MD, Graff LA, Shen B. Symptomatology of irritable bowel syndrome and inflammatory bowel disease during the menstrual cycle. *Gastroenterol Rep (Oxf)*. 2015;3(3):185-193.

120. Frändemark Å, Ung EJ, Törnblom H, Simrén M, Jakobsson S. Fatigue: a distressing symptom for patients with irritable bowel syndrome. *Neurogastroenterol Motil*. 2017;29(1).

121. Rome Foundation. Available at https://theromefoundation.org. Last accessed November 12, 2022.

122. Lacy BE. Perspective: an easier diagnosis. *Nature*. 2016;533(7603):S107.

123. Longstreth GF, Thompson WG, Chey WD, Houghton LA, Mearin F, Spiller RC. Functional bowel disorders. *Gastroenterology*. 2006;130(5):1480-1491.

124. Lewis SJ, Heaton KW. Stool form scale as a useful guide to intestinal transit time. *Scand J Gastroenterol*. 1997;32(9):920-924.

125. Mayer EA. Irritable bowel syndrome. *N Engl J Med*. 2008;358(16):1692-1699.

126. Brandt LJ, Chey WD, Foxx-Orenstein AE, et al. An evidence-based position statement on the management of irritable bowel syndrome. *Am J Gastroenterol*. 2009;104(Suppl 1):S1-S35.

127. Spiller R, Lam C. The shifting interface between IBS and IBD. *Curr Opin Pharmacol*. 2011;11(6):586-592.

128. Berrill JW, Green JT, Hood K, Campbell AK. Symptoms of irritable bowel syndrome in patients with inflammatory bowel disease: examining the role of sub-clinical inflammation and the impact on clinical assessment of disease activity. *Aliment Pharmacol Ther*. 2013;38(1):44-51.

129. Chey WD, Nojkov B, Rubenstein JH, et al. The yield of colonoscopy in patients with non-constipated irritable bowel syndrome: results from a prospective, controlled US trial. *Am J Gastroenterol*. 2010;105(4):859-865.

130. Menees SB, Kurlander J, Goel A, Powell CC, Chey WD. A meta-analysis of the utility of common serum and fecal biomarkers in adults with IBS. *Gastroenterology*. 2014;146(5):S194.

131. Wald A, Bharucha AE, Cosman BC, Whitehead WE. ACG clinical guideline: management of benign anorectal disorders. *Am J Gastroenterol*. 2014;109(8):1141-1157.

132. Ratuapli SK, Bharucha AE, Noelting J, Harvey DM, Zinsmeister AR. Phenotypic identification and classification of functional defecatory disorders using high-resolution anorectal manometry. *Gastroenterology*. 2013;144(2):314-322.

133. Chey WD, Baker JRB, Shifferd J. Assessment of abdominal symptoms before and after biofeedback therapy in patients with dyssynergic defecation. *Am J Gastroenterol*. 2012;107(suppl 1):S718.

134. Spiegel BM, Farid M, Esrailian E, Talley J, Chang L. Is irritable bowel syndrome a diagnosis of exclusion? A survey of primary care providers, gastroenterologists, and IBS experts. *Am J Gastroenterol*. 2010;105(4):848-858.

135. Drossman DA. The functional gastrointestinal disorders and the Rome III process. *Gastroenterology*. 2006;130(5):1377-1390.

136. Verghese A, Brady E, Kapur CC, Horwitz RI. The bedside evaluation: ritual and reason. *Ann Intern Med*. 2011;155(8):550-553.

137. Johannesson E, Simrén M, Strid H, Bajor A, Sadik R. Physical activity improves symptoms in irritable bowel syndrome: a randomized controlled trial. *Am J Gastroenterol*. 2011;106(5):915-922.

138. Daley AJ, Grimmett C, Roberts L, et al. The effects of exercise upon symptoms and quality of life in patients diagnosed with irritable bowel syndrome: a randomised controlled trial. *Int J Sports Med*. 2008;29(9):778-782.

139. Kuttner L, Chambers CT, Hardial J, Israel DM, Jacobson K, Evans K. A randomized trial of yoga for adolescents with irritable bowel syndrome. *Pain Res Manag*. 2006;11(4):217-223.

140. Buchanan DT, Cain K, Heitkemper M, et al. Sleep measures predict next-day symptoms in women with irritable bowel syndrome. *J Clin Sleep Med*. 2014;10(9):1003-1009.

141. Berrill JW, Sadlier M, Hood K, Green JT. Mindfulness-based therapy for inflammatory bowel disease patients with functional abdominal symptoms or high perceived stress levels. *J Crohns Colitis*. 2014;8(9):945-955.

142. Chapman RW, Stanghellini V, Geraint M, Halphen M. Randomized clinical trial: macrogol/PEG 3350 plus electrolytes for treatment of patients with constipation associated with irritable bowel syndrome. *Am J Gastroenterol*. 2013;108(9):1508-1515.

143. Madsen JL, Linnet J, Rumessen JJ. Effect of nonabsorbed amounts of a fructose-sorbitol mixture on small intestinal transit in healthy volunteers. *Dig Dis Sci*. 2006;51(1):147-153.

144. Murray K, Wilkinson-Smith V, Hoad C, et al. Differential effects of FODMAPs (fermentable oligo-, di-, mono-saccharides and polyols) on small and large intestinal contents in healthy subjects shown by MRI. *Am J Gastroenterol*. 2014;109(1):110-119.

145. Itan Y, Jones BL, Ingram CJ, et al. A worldwide correlation of lactase persistence phenotype and genotypes. *BMC Evol Biol.* 2010;10:36.
146. Casellas F, Aparici A, Casaus M, Rodriguez P, Malagelada JR. Subjective perception of lactose intolerance does not always indicate lactose malabsorption. *Clin Gastroenterol Hepatol.* 2010;8(7):581-586.
147. Moayyedi P, Quigley EM, Lacy BE, et al. The effect of dietary intervention on irritable bowel syndrome: a systematic review. *Clin Transl Gastroenterol.* 2015;6:e107.
148. Halmos EP, Power VA, Shepherd SJ, Gibson PR, Muir JG. A diet low in FODMAPs reduces symptoms of irritable bowel syndrome. *Gastroenterology.* 2014;146(1):67-75.
149. Biesiekierski JR, Peters SL, Newnham ED, Rosella O, Muir JG, Gibson PR. No effects of gluten in patients with self-reported non-celiac gluten sensitivity after dietary reduction of fermentable, poorly absorbed, short-chain carbohydrates. *Gastroenterology.* 2013;145(2):320-328.
150. Bull MJ, Plummer NT. Part 2: Treatments for chronic gastrointestinal disease and gut dysbiosis. *Integr Med (Encinitas).* 2015;14(1):25-33.
151. Bernet MF, Brassart D, Neeser JR, Servin AL. Lactobacillus-acidophilus LA-1 binds to cultured human intestinal-cell lines and inhibits cell attachment and cell invasion by enterovirulent bacteria. *Gut.* 1994;35(4):483-489.
152. O'Mahony L, McCarthy J, Kelly P, et al. Lactobacillus and bifidobacterium in irritable bowel syndrome: symptom responses and relationship to cytokine profiles. *Gastroenterology.* 2005;128(3):541-551.
153. Whorwell PJ, Altringer L, Morel J, et al. Efficacy of an encapsulated probiotic *Bifidobacterium infantis* 35624 in women with irritable bowel syndrome. *Am J Gastroenterol.* 2006;101(7):1581-1590.
154. Zhang Y, Li L, Guo C, et al. Effects of probiotic type, dose and treatment duration on irritable bowel syndrome diagnosed by Rome III criteria: a meta-analysis. *BMC Gastroenterol.* 2016;16(1):62.
155. Wegener ST, Castillo RC, Haythornthwaite J, Mackenzie EJ, Bosse MJ. Psychological distress mediates the effect of pain on function. *Pain.* 2011;152(6):1349-1357.
156. Leung L. Pain catastrophizing: an updated review. *Indian J Psychol Med.* 2012;34(3):204-217.
157. Levy RL, Langer SL, Walker LS, et al. Cognitive-behavioral therapy for children with functional abdominal pain and their parents decreases pain and other symptoms. *Am J Gastroenterol.* 2010;105(4):946-956.
158. Nezu AM, Ronan GF. Life stress, current problems, problem solving, and depressive symptoms: an integrative model. *J Consult Clin Psychol.* 1985;53(5):693-697.
159. Keefer L, Blanchard EB. The effects of relaxation response meditation on the symptoms of irritable bowel syndrome: results of a controlled treatment study. *Behav Res Ther.* 2001;39(7):801-811.
160. Rokicki LA, Holroyd KA, France CR, Lipchik GL, France JL, Kvaal SA. Change mechanisms associated with combined relaxation/EMG biofeedback training for chronic tension headache. *Appl Psychophysiol Biofeedback.* 1997;22(1):21-41.
161. Fried R. Role of respiration in stress and stress control: toward a theory of stress as a hypoxic phenomenon. In: Lehrer PM, Woolfolk RL (eds). *Principles and Practice of Stress Management.* 2nd ed. New York, NY: Guilford; 1993: 301-333.
162. Gaylord SA, Palsson OS, Garland EL, et al. Mindfulness training reduces the severity of irritable bowel syndrome in women: results of a randomized controlled trial. *Am J Gastroenterol.* 2011;106(9):1678-1688.
163. Zernicke KA, Campbell TS, Blustein PK, et al. Mindfulness-based stress reduction for the treatment of irritable bowel syndrome symptoms: a randomized wait-list controlled trial. *Int J Behav Med.* 2013;20(3):385-396.
164. Whorwell PJ, Prior A, Faragher EB. Controlled trial of hypnotherapy in the treatment of severe refractory irritable bowel syndrome. *Lancet.* 1984;2(8414):1232-1234.
165. Ford AC, Quigley EM, Lacy BE, et al. Effect of antidepressants and psychological therapies, including hypnotherapy, in irritable bowel syndrome: systematic review and meta-analysis. *Am J Gastroenterol.* 2014;109(9):1350-1365.
166. Craske MG, Wolitzky-Taylor KB, Labus J, et al. A cognitive-behavioral treatment for irritable bowel syndrome using interoceptive exposure to visceral sensations. *Behav Res Ther.* 2011;49(6-7):413-421.
167. Ljotsson B, Hesser H, Andersson E, et al. Mechanisms of change in an exposure-based treatment for irritable bowel syndrome. *J Consult Clin Psychol.* 2013;81(6):1113-1126.
168. Boersma K, Ljótsson B, Edebol-Carlman H, Schrooten M, Linton SJ, Brummer RJ. Exposure-based cognitive behavioral therapy for irritable bowel syndrome: a single-case experimental design across 13 subjects. *Cogn Behav Ther.* 2016;45(6):415-430.
169. Ford AC, Talley NJ, Schoenfeld PS, Quigley EMM, Moayyedi P. Efficacy of antidepressants and psychological therapies in irritable bowel syndrome: systematic review and meta-analysis. *Gut.* 2009;58(3):367-378.
170. Lackner JM, Morley S, Mesmer C, Dowzer C, Hamilton S. Psychological treatments for irritable bowel syndrome: a systematic review and meta-analysis. *J Consult Clin Psychol.* 2004;72(6):1100-1113.
171. Ljótsson B, Hedman E, Andersson E, et al. Internet-delivered exposure-based treatment vs. stress management for irritable bowel syndrome: a randomized trial. *Am J Gastroenterol.* 2011;106(8):1481-1491.
172. Laird KT, Tanner-Smith EE, Russell AC, Hollon SD, Walker LS. Short-term and long-term efficacy of psychological therapies for irritable bowel syndrome: a systematic review and meta-analysis. *Clin Gastroenterol Hepatol.* 2016;14(7):937-947.

173. Dekel R, Drossman DA, Sperber AD. The use of psychotropic drugs in irritable bowel syndrome. *Expert Opin Investig Drugs*. 2013;22(3):329-339.

174. Drossman DA. Beyond tricyclics: new ideas for treating patients with painful and refractory functional gastrointestinal symptoms. *Am J Gastroenterol*. 2009;104(12):2897-2902.

175. Mico JA, Ardid D, Berrocoso E, Eschaller A. Antidepressants and pain. *Trends Pharmacol Sci*. 2006;27(7):348-354.

176. Halpert A, Dalton CB, Diamant NE, et al. Clinical response to tricyclic antidepressants in functional bowel disorders is not related to dosage. *Am J Gastroenterol*. 2005;100(3):664-671.

177. Vahedi H, Merat S, Momtahen S, et al. Clinical trial: the effect of amitriptyline in patients with diarrhoea-predominant irritable bowel syndrome. *Aliment Pharmacol Ther*. 2008;27(8):678-684.

178. Grover M, Camilleri M. Effects on gastrointestinal functions and symptoms of serotonergic psychoactive agents used in functional gastrointestinal diseases. *J Gastroenterol*. 2013;48(2):177-181.

179. Goldapple K, Segal Z, Garson C, et al. Modulation of cortical-limbic pathways in major depression: treatment-specific effects of cognitive behavior therapy. *Arch Gen Psychiatry*. 2004;61(1):34-41.

180. Keller MB, McCullough JP, Klein DN, et al. A comparison of nefazodone, the cognitive behavioral-analysis system of psychotherapy, and their combination for the treatment of chronic depression. *N Engl J Med*. 2000;342(20):1462-1470.

181. Holroyd KA, O'Donnell FJ, Stensland J, Lipchik GL, Cordingley GE, Carlson BW. Management of chronic tension-type headache with tricyclic antidepressant medication, stress management therapy, and their combination. *JAMA*. 2001;285(17):2208-2215.

182. Creed F, Fernandes L, Guthrie E, et al. The cost-effectiveness of psychotherapy and paroxetine for severe irritable bowel syndrome. *Gastroenterol*. 2003;124(2):303-317.

183. Lee KJ. Pharmacologic agents for chronic diarrhea. *Intest Res*. 2015;13(4):306-312.

184. Iorio N, Malik Z, Schey R. Profile of rifaximin and its potential in the treatment of irritable bowel syndrome. *Clin Exp Gastroenterol*. 2015;8:159-167.

185. Pimentel M, Chang C, Chua KS, et al. Antibiotic treatment of constipation-predominant irritable bowel syndrome. *Dig Dis Sci*. 2014;59(6):1278-1285.

186. International Foundation for Functional Gastrointestinal Disorders. Medications for IBS. Available at https://aboutibs.org/treatment/medications-for-ibs. Last accessed November 12, 2022.

187. Min YW, Rhee PL. The clinical potential of ramosetron in the treatment of irritable bowel syndrome with diarrhea (IBS-D). *Therap Adv Gastroenterol*. 2015;8(3):136-142.

188. U.S. Food and Drug Administration. Alosetron REMS Program: Safety Information Fact Sheet for Prescribers. Available at https://www.accessdata.fda.gov/drugsatfda_docs/rems/alosetron_2016-03-24_Safety_Information_Fact_Sheet.pdf. Last accessed November 12, 2022.

189. CenterWatch. FDA Approved Drugs for Gastroenterology. Available at https://www.centerwatch.com/directories/1067-fda-approved-drugs/topic/96-gastroenterology. Last accessed November 12, 2022.

190. Lembo AJ, Lacy BE, Zuckerman MJ, et al. Eluxadoline for irritable bowel syndrome with diarrhea. *N Engl J Med*. 2016;374(3):242-253.

191. Guilarte M, Santos J, de Torres I, et al. Diarrhoea-predominant IBS patients show mast cell activation and hyperplasia in the jejunum. *Gut*. 2007;56(2):203-209.

192. Camilleri M. Current and future pharmacological treatments for diarrhea-predominant irritable bowel syndrome. *Expert Opin Pharmacother*. 2013;14(9):1151-1160.

193. Leri O, Tubili S, De Rosa FG, et al. Management of diarrhoeic type of irritable bowel syndrome with exclusion diet and disodium cromoglycate. *Inflammopharmacology*. 1997;5(2):153-158.

194. Lobo B, Vicario M, Martinez C, et al. Clinical improvement in IBS after disodium cromoglycate involves mast cell-mediated toll-like receptor signaling downregulation. *Gastroenterology*. 2011;140(Suppl 1):499-500.

195. Klooker TK, Braak B, Koopman KE, et al. The mast cell stabilizer ketotifen decreases visceral hypersensitivity and improves intestinal symptoms in patients with irritable bowel syndrome. *Gut*. 2010;59(9):1213-1221.

196. Clavé P, Acalovschi M, Triantafillidis JK. Randomised clinical trial: otilonium bromide improves frequency of abdominal pain, severity of distention and time to relapse in patients with irritable bowel syndrome. *Aliment Pharmacol Ther*. 2011;34(4):432-442.

197. Basra S, Verne GN, Zhou Q. Randomized placebo-controlled trial of glutamine for the treatment of diarrhea-predominant irritable bowel syndrome. *Gastroenterology*. 2013;144(5 Suppl 1):S160.

198. Cash BD, Lacy BE, Rao T, Earnest DL. Rifaximin and eluxadoline: newly approved treatments for diarrhea-predominant irritable bowel syndrome: what is their role in clinical practice alongside alosetron? *Expert Opin Pharmacother*. 2016;17(3):311-322.

199. Wilson N, Schey R. Lubiprostone in constipation: clinical evidence and place in therapy. *Ther Adv Chronic Dis*. 2015;6(2):40-50.

200. Manabe N, Rao AS, Wong BS, Camilleri M. Emerging pharmacologic therapies for irritable bowel syndrome. *Curr Gastroenterol Rep*. 2010;12(5):408-416.

201. Thomas RH, Luthin DR. Current and emerging treatments for irritable bowel syndrome with constipation and chronic idiopathic constipation: focus on prosecretory agents. *Pharmacotherapy*. 2015;35(6):613-630.

202. Hayase M, Hashitani H, Suzuki H, Kohri K, Branding AF. Evolving mechanisms of action of alverine citrate on phasic smooth muscles. *Br J Pharmacol*. 2007;152(8):1228-1238.

203. Ford A, Moayyedi P, Lacy B, et al. American College of Gastroenterology monograph on the management of irritable bowel syndrome and chronic idiopathic constipation. *Am J Gastroenterol*. 2014;109(Suppl 1):S2-S26.

204. Ford AC, Talley NJ, Spiegel BMR, et al. Effect of fibre, antispasmodics, and peppermint oil in the treatment of irritable bowel syndrome: systematic review and meta-analysis. *BMJ*. 2008;337:a2313.

205. Houghton LA, Fell C, Whorwell PJ, Jones I, Sudworth DP, Gale JD. Effect of a second-generation alpha2delta ligand (pregabalin) on visceral sensation in hypersensitive patients with irritable bowel syndrome. *Gut*. 2007;56(9):1218-1225.

206. van Wanrooij S, Wouters MM, Van Oudenhove L, Vermeire S, Rutgeerts PJ, Boeckxstaens GE. Effect of the H1-receptor antagonist ebastin on visceral perception and clinical symptoms in IBS. *Gastroenterology*. 2013;144(5 Suppl 1):S160.

207. Barshop K, Staller K. New pathways, new targets: visceral hypersensitivity pathogenesis in irritable bowel syndrome. *Clin Transl Gastroenterol*. 2016;7(2):e146.

208. LeBeau S, Khoruts A. Fecal microbiota transplantation: an interview with Alexander Khoruts. *Global Adv Health Med*. 2014;3(3):73-80.

209. Smally W, Faick-Yyyer C, Carrasco-Labra A, et al. American Gastroenterological Association clinical practice guidelines on the laboratory evaluation of functional diarrhea and diarrhea-predominant irritable bowel syndrome in adults (IBS-D). *Gastroenterology*. 2019;157:851-854.

210. Thakur ER, Shapiro J. Chan J, et al. A systematic review of the effectiveness of psychological treatments for IBS in gastroenterology settings: promising but in need of further study. *Dig Dis Sci*. 2018;63:2189-2201.

211. Halkjaer SI, Christensen AH, Lo B, et al. Fecal microbiota transplantation alters gut microbiota in patients with irritable bowel syndrome: results of a randomized, double-blind, placebo-controlled study. *Gut*. 2018;67:2107-2115.

212. Xu D, Chen VL, Steiner, CA, et al. Efficacy of fecal microbiota transplantation in irritable bowel syndrome: a systematic review and meta-analysis. *Am J Gasroenterol*. 2019;114:1043-1050.

213. Paisson OS, Whitehead W, Tomblom H, et al. Prevalence of Rome IV functional bowel disorders among adults in the United States, Canada, and the United Kingdom. *Gastroenterology*. 2020;158:1262-1273.

214. Sperber AD, Bangdiwala SI, Drossman DA, et al. Worldwide prevalence and burden of functional gastrointestinal disorders, results of Rome Foundation Global Study. *Gastroenterology*. 2021;160:99-114.

215. Chey WD, Hashash JG, Manning L, et al. AGA clinical practice update on the role of diet in irritable bowel syndrome: expert review. *Gastroenteroogyogyl*. 2022;162:1737-1745.

216. Caselli M, Cassol F, Calo G, et al. Actual concept of "probiotics:" is it more functional to science or business? *J Gastroenterology*. 2013;19:1527-1540.

217.Su GL, Ko CW, Bercik P, et al. AGA clinical practice guidelines on the role of probiotics in the management of gastrointestinal disorders. *Gastroenterologyl*. 2020;159:697-705.

218. Lembo A, Sultan S, Chang L, et al. AGA clinical practice guideline on the pharmacological management of irritable bowel syndrome with diarrhea. *Gastroenterology*. 2022;163:137-151.

219. Chang L, Sultan S, Lembo A, et al. AGA clinical practice guideline on the pharmacological management of irritable bowel syndrome with constipation. *Gastroenterology*. 2022;163:118-136.

220. Lacy BE, Pimentel M, Brenner DM, et. al. ACG clinical guideline: management of irritable bowel syndrome. *Am J Gastroenterol*. 2021;116:17-44.

221. Tack J, Stanghellini V, Mearin F, et al. Economic burden of moderate to severe irritable bowel syndrome with constipation in six European countries. *BMC Gastroenterology*. 2019;19(69).

Evidence-Based Practice Recommendations Citations

National Collaborating Centre for Nursing and Supportive Care. *Irritable Bowel Syndrome in Adults: Diagnosis and Management of Irritable Bowel Syndrome in Primary Care*. London: National Institute for Health and Care Excellence; 2017. Available at https://www.nice.org.uk/guidance/cg61. Last accessed November 18, 2022.

Lembo A, Sultan S, Chang L, Heidelbaugh JJ, Smalley W, Verne GN. AGA clinical practice guideline on the pharmacological management of irritable bowel syndrome with diarrhea. *Gastroenterology*. 2022;163(1):137-151. Available at https://www.gastrojournal.org/article/S0016-5085(22)00391-2/fulltext. Last accessed November 18, 2022.

Chang L, Sultan S, Lembo A, Verne GN, Smalley W, Heidelbaugh JJ. AGA clinical practice guideline on the pharmacological management of irritable bowel syndrome with constipation. *Gastroenterology*. 2022;163(1):118-136. Available at https://www.gastrojournal.org/article/S0016-5085(22)00390-0/fulltext. Last accessed November 18, 2022.