Review

Irritable Bowel Syndrome
A Clinical Review

William D. Chey, MD; Jacob Kurlander, MD; Shanti Eswaran, MD

IMPORTANCE Irritable bowel syndrome (IBS) affects 7% to 21% of the general population. It is a chronic condition that can substantially reduce quality of life and work productivity.

OBJECTIVES To summarize the existing evidence on epidemiology, pathophysiology, and diagnosis of IBS and to provide practical treatment recommendations for generalists and specialists according to the best available evidence.

EVIDENCE REVIEW A search of Ovid (MEDLINE) and Cochrane Database of Systematic Reviews was performed for literature from 2000 to December 2014 for the terms *pathophysiology*, *etiology*, *pathogenesis*, *diagnosis*, *irritable bowel syndrome*, and *IBS*. The range was expanded from 1946 to December 2014 for *IBS*, *irritable bowel syndrome*, *diet*, *treatment*, and *therapy*.

FINDINGS The database search yielded 1303 articles, of which 139 were selected for inclusion. IBS is not a single disease but rather a symptom cluster resulting from diverse pathologies. Factors important to the development of IBS include alterations in the gut microbiome, intestinal permeability, gut immune function, motility, visceral sensation, brain-gut interactions, and psychosocial status. The diagnosis of IBS relies on symptom-based criteria, exclusion of concerning features (symptom onset after age 50 years, unexplained weight loss, family history of selected organic gastrointestinal diseases, evidence of gastrointestinal blood loss, and unexplained iron-deficiency anemia), and the performance of selected tests (complete blood cell count, C-reactive protein or fecal calprotectin, serologic testing for celiac disease, and age-appropriate colorectal cancer screening) to exclude organic diseases that can mimic IBS. Determining the predominant symptom (IBS with diarrhea, IBS with constipation, or mixed IBS) plays an important role in selection of diagnostic tests and treatments. Various dietary, lifestyle, medical, and behavioral interventions have proven effective in randomized clinical trials.

CONCLUSIONS AND RELEVANCE The diagnosis of IBS relies on the identification of characteristic symptoms and the exclusion of other organic diseases. Management of patients with IBS is optimized by an individualized, holistic approach that embraces dietary, lifestyle, medical, and behavioral interventions.

JAMA. 2015;313(9):949-958. doi:10.1001/jama.2015.0954

Author Affiliations: Division of Gastroenterology, University of Michigan Health System, Ann Arbor.

Corresponding Author: William D. Chey, MD, GI Physiology Laboratory, Michigan Bowel Control Program, University of Michigan Health System, 3912 Taubman Center, SPC 5362, Ann Arbor, MI 48109-5362 (wchey@med.umich.edu).

Section Editor: Mary McGrae McDermott, MD, Senior Editor.

Irritable bowel syndrome (IBS) is the most commonly diagnosed gastrointestinal condition. It is a symptom-based condition defined by the presence of abdominal pain or discomfort, with altered bowel habits, in the absence of any other disease to cause these sorts of symptoms. Pooled population-based prevalence estimates of IBS vary globally, in part related to differences in study populations, diagnostic criteria, and study methodology. In North America, the population prevalence of IBS is approximately 12%.[1] IBS is most prevalent in South America (21.0%) and least prevalent in Southeast Asia (7.0%).[1] In the United States, Canada, and Israel, IBS symptoms are 1.5 to 2 times more prevalent among women than men, whereas there appears to be greater parity in Asia.[2] Women more commonly report abdominal pain and constipation, whereas men more commonly report diarrhea.[2] It appears that IBS prevalence decreases with age. In the United States, patients are equally distributed among IBS with diarrhea (IBS-D), IBS with constipation (IBS-C), and IBS with a mixed bowel pattern (IBS-M), whereas in Europe, IBS-C or IBS-M may be more prevalent.[3]

This clinical review covers the epidemiology, natural history, pathophysiology, diagnosis, and management of IBS.

Methods

Evidence to support this clinical review was obtained from searches performed by a medical librarian of MEDLINE and the Cochrane Database of Systematic Reviews from 2000 to December 2014 for the terms *pathophysiology, etiology, pathogenesis, diagnosis, irritable bowel syndrome,* and *IBS*. The range was expanded from 1946 to December 2014 for *IBS, irritable bowel syndrome, diet, treatment,* and *therapy*. This search strategy yielded 1303 articles after limiting to the English language. We selected 139 articles for inclusion. When available, systematic reviews and meta-analyses were used to summarize the available evidence.

FODMAP *fermentable oligosaccharides, disaccharides, monosaccharides, and polyols*

IBS *irritable bowel syndrome*

IBS-C *IBS with constipation*

IBS-D *IBS with diarrhea*

IBS-M *IBS with a mixed bowel pattern*

Burden of Illness and Natural History

Multiple comorbidities are associated with IBS, including somatic pain syndromes (fibromyalgia, chronic fatigue syndrome, and chronic pelvic pain),[4] other gastrointestinal disorders (gastroesophageal reflux disease[5] and dyspepsia[6]), and psychiatric disorders (major depression, anxiety, and somatization),[7] raising the possibility of shared pathogenesis.

In most patients, IBS is a chronic relapsing disease in which symptoms may vary over time. A systematic review showed that during long-term follow-up of clinic-based IBS patients, 2% to 18% worsened, 30% to 50% remained unchanged, and 12% to 38% improved.[8] Previous surgery, longer duration of disease, higher somatic scores, and comorbid anxiety and depression all predicted worse outcomes. After a negative diagnostic evaluation result, a patient receiving a diagnosis of IBS has a less than 5% risk of receiving an alternative organic diagnosis in the future.[8]

Over time, patients may migrate between different IBS subtypes,[9] most commonly from IBS-C or IBS-D to IBS-M; switching between IBS-C and IBS-D occurs less commonly.[10] Many of the "natural history" studies in IBS are affected by treatments introduced by the patient or clinician. Thus, it is difficult to know how much symptom variation is the consequence of medical intervention vs the true natural history of IBS.

IBS significantly reduces health-related quality of life and work productivity.[11] Among patients with IBS, 13% to 88% seek care. Individuals who seek care have more distress and less social support than those who do not.[12] In the United States, IBS accounts for 3.1 million ambulatory care visits and 5.9 million prescriptions annually, with total direct and indirect expenditures exceeding $20 billion.[13,14]

Pathophysiology

The pathogenesis of IBS, like the clinical phenotype, is heterogeneous (**Box 1**). IBS likely encompasses a number of diseases with dis-

---

Box 1. Pathophysiology of Irritable Bowel Syndrome (IBS)

Environmental Contributors to IBS Symptoms
Early life stressors (abuse, psychosocial stressors)

Food intolerance

Antibiotics

Enteric infection

Host Factors Contributing to IBS Symptoms
Altered pain perception

Altered brain-gut interaction

Dysbiosis

Increased intestinal permeability

Increased gut mucosal immune activation

Visceral hypersensitivity

---

tinct pathophysiology that present with similar symptoms. During the past 40 years, a number of factors that contribute to the pathophysiology of IBS have emerged. Traditionally, the pathogenesis of IBS has focused on abnormalities in motility, visceral sensation, brain-gut interaction, and psychosocial distress. Although one or more of these abnormalities are demonstrable in the majority of IBS patients, none can account for symptoms in all of them. More recently, altered gut immune activation, intestinal permeability, and intestinal and colonic microbiome have been identified in some IBS patients.[15,16]

Supporting a role for these factors is the increased prevalence of IBS symptoms in inflammatory conditions such as celiac disease[17] and inflammatory bowel diseases[18] and following severe acute gastroenteritis.[19] The intestinal mucosa of some IBS patients shows increased activation of the innate and adaptive immune systems.[20,21] Increased small bowel and colonic permeability has also been observed in patients with IBS-D[22] and is associated with visceral hypersensitivity.[23] The fecal microbiota of IBS patients differ significantly from that of controls, likely reflecting the influence of genetics, diet, stress, infection, and drugs or antibiotics.[24]

IBS symptoms that arise after acute gastroenteritis or so-called postinfectious IBS present an interesting developmental model. Host factors such as genetics, immune function, microbiome, and psychological status, as well as environmental factors such as stress, severity of infection, or treatment with antibiotics, could predispose to the development of chronic IBS symptoms.[25] It is important to identify patients with postinfectious IBS because, unlike typical IBS, which tends to be a chronic relapsing condition, it spontaneously resolves in roughly half of patients within 6 to 8 years of the index infection.[25]

Many patients identify food as a trigger for their IBS symptoms. Various reviews of how specific dietary constituents can cause gastrointestinal symptoms are available.[26-29] The contribution of true food allergies to IBS is small.[30] Conversely, food intolerances are common in IBS patients. Increasingly, rapidly fermentable, osmotically active, short-chain carbohydrates (including fructose, lactose, fructans and galactans, and sugar alcohols) have been recognized as an important trigger of IBS symptoms. Poorly absorbed carbohydrates can exert osmotic effects and lead to increased fermentation in the small bowel or colon, which can exacerbate symptoms

Box 2. Features of Irritable Bowel Syndrome

Typical Features
Loose/frequent stools

Constipation

Bloating

Abdominal cramping, discomfort, or pain

Symptom brought on by food intake/specific food sensitivities

Symptoms dynamic over time (change in pain location, change in stool pattern)

Concerning Features for Organic Disease
Symptom onset after age 50 y

Severe or progressively worsening symptoms

Unexplained weight loss

Nocturnal diarrhea

Family history of organic gastroenterological diseases, including colon cancer, celiac disease, or inflammatory bowel disease

Rectal bleeding or melena

Unexplained iron-deficiency anemia

Box 3. Rome III Criteria for Irritable Bowel Syndrome (IBS) With Subtypes[a]

Recurrent abdominal pain or discomfort[b] at least 3 d/mo in the last 3 mo associated with 2 or more of the following:

1. Improvement with defecation

2. Onset associated with a change in frequency of stool

3. Onset associated with a change in form (appearance) of stool

Subtyping IBS by Predominant Stool Pattern
1. IBS with constipation—hard or lumpy stools ≥25% and loose or watery stools <25% of bowel movements

2. IBS with diarrhea—loose or watery stools ≥25% and hard or lumpy stools <25% of bowel movements

3. Mixed IBS—hard or lumpy stools ≥25% and loose or watery stools ≥25% of bowel movements

[a] Criterion fulfilled for the last 3 months, with symptom onset at least 6 months before diagnosis.

[b] "Discomfort" means an uncomfortable sensation not described as pain.

in IBS patients who have underlying abnormalities in gut function and sensation.[29] On the other hand, healthy individuals with normal gut function and sensation rarely experience symptoms after a meal.

Psychosocial factors may also predispose to the development of IBS. Women with IBS are more likely to have experienced verbal, sexual, or physical abuse, which can contribute to the development of the disease through brain-gut and mucosal immune dysfunction.[31] For some IBS patients, recurrent abdominal pain may begin in childhood and reflect learned-illness behaviors.[32] These experiences may lead to persistent changes in the brain-gut axis, resulting in the perception of otherwise unconscious interoceptive input from the gastrointestinal tract.[33] A subset of IBS patients have hypersensitivity to rectal balloon distention and increased activation of brain regions associated with emotional arousal and endogenous pain modulation.[34] In another subset of IBS patients, hypervigilance and catastrophizing are important features that lead to gastrointestinal and nongastrointestinal symptom amplification.[35]

Diagnosis

The diagnosis of IBS is based on the presence of characteristic symptoms and the exclusion of selected organic diseases (**Box 2**). The cardinal features of IBS according to the current diagnostic standard, the Rome III criteria, include abdominal pain or discomfort and altered bowel habits (**Box 3**). IBS patients can experience constipation, diarrhea, or both. Identification of a patient's predominant bowel complaint plays an important role in both the selection of diagnostic testing and treatment. The Rome III criteria emphasize the importance of stool consistency to distinguish between the 3 subtypes of IBS (Box 3)[36] because it correlates with patients' complaints of constipation or diarrhea and colonic transit better than stool frequency.[37] It can be assessed with the Bristol

Stool Form Scale, a validated instrument that allows reporting of stool appearance from a score of 1 (hard and lumpy stool) to 7 (entirely liquid).[38] Bloating (subjective sensation of abdominal fullness) and distention (objective increase in abdominal girth) are also common and bothersome complaints reported by more than 80% of IBS patients.[39] However, many individuals without IBS also report these complaints.[40]

Although identifying patients with IBS-D or IBS-C is straightforward, patients with IBS-M present unique challenges. A detailed history can help determine whether a mixed bowel pattern represents the underlying disease state or is the consequence of medical intervention. It is important to consider all prescription and over-the-counter medications and supplements that could affect IBS symptoms (**Box 4**). A stool diary can help identify patterns among the chaotic bowel habits that many IBS patients report. Many IBS-M patients report periods without a bowel movement or with only small, hard stools, followed by periods of multiple stools of variable consistency that they interpret as "diarrhea." Most of these patients actually have IBS-C, with periods of progressive stool accumulation culminating in bowel purging. A radiograph demonstrating fecal loading can help confirm this clinical suspicion.

Along with an assessment of symptom-based criteria, one should be conducted for the presence of concerning features that identify patients who should undergo a more detailed evaluation to exclude organic disease[41] (Box 2, **Box 5**). Although the presence of concerning features may identify patients more likely to have an organic disease, most patients will ultimately have a negative evaluation result. Thus, the value of concerning features lies in their negative, rather than their positive, predictive value. Evidence suggests that a diagnosis of IBS can be confidently made for patients who fulfill symptom-based criteria and have no concerning features because the yield of extensive diagnostic testing is low.[42] Nonetheless, most health care professionals view IBS as a diagnosis of exclusion[43] and are uncomfortable relying solely on symptoms to diagnose it.

There are several diseases that should be considered in patients with IBS symptoms. A meta-analysis of 5 studies found a 4-fold

Box 4. Commonly Used Treatments That Can Exacerbate Irritable
Bowel Syndrome Symptoms

Over-the-Counter
Antihistamines

Calcium

Iron

Magnesium

Nonsteroidal anti-inflammatory drugs

Wheat bran

Prescription
Antibiotics

Antidepressants

Antiparkinsonian drugs

Antipsychotics

Calcium-channel blockers

Diuretics

Metformin

Opioids

Sympathomimetics

Box 5. Diagnostic Testing for Patients With Suspected Irritable
Bowel Syndrome (IBS) and No Concerning Features

All IBS Subtypes
Complete blood cell count

Age-appropriate colorectal cancer screening

IBS With Diarrhea
C-reactive protein or fecal calprotectin

IgA TtG +/− quantitative IgA

When colonoscopy performed, obtain random biopsies

SeHCAT, fecal bile acids, or serum C_4 where available

IBS, Mixed
C-reactive protein or fecal calprotectin

IgA TtG +/− quantitative IgA

Stool diary

Consider abdominal radiography to evaluate for stool accumulation

IBS With Constipation
If severe or medically refractory, refer to gastroenterology specialist
for physiologic testing

Abbreviations: SeHCAT, tauroselcholic (selenium 75) acid; TtG, tissue translutaminase.

---

increased likelihood of biopsy-proven celiac disease in patients with IBS symptoms.[44] The prevalence of celiac disease in these patients varies by region, and although studies from Europe have demonstrated a higher prevalence of the disease, those from the United States have not.[45] Decision analysis suggests that routine screening for celiac disease in IBS patients becomes cost-effective at a prevalence of greater than or equal to 1%.[46] Given the potential long-term consequences of missing celiac disease, clinicians caring for patients with IBS should have a low threshold to screen for it, particularly in individuals with IBS-D.[41]

Recent literature has identified that a small subset of patients with suspected IBS-D have microscopic colitis. A recent case-control study found that age older than 50 years, nocturnal stools, weight loss, shorter duration of diarrhea, recent introduction of new drugs, and comorbid autoimmune diseases were associated with an increased risk of microscopic colitis (Box 2).[47] When colonoscopy is performed in patients with suspected IBS-D, random colon biopsies should be performed to rule out microscopic colitis (Box 5).[41]

Inflammatory bowel diseases, including ulcerative colitis and Crohn disease, are of concern when a patient with IBS symptoms is evaluated. Even low-grade inflammation could alter permeability and sensitize visceral afferent neurons, leading to alterations in motility and visceral sensation.[18] Studies suggest that more than a third of patients with inflammatory bowel disease fulfill the Rome criteria for IBS.[18] It is unclear how many patients with inflammatory bowel disease and overlapping IBS symptoms have concerning features (Box 2). From a pragmatic standpoint, the important question is how often inflammatory bowel disease is ultimately identified in patients who have typical IBS symptoms and no concerning features. A prospective US study that included more than 900 nonconstipated IBS patients and healthy controls undergoing colonoscopy found inflammatory bowel disease in less than 1% of IBS patients and none of the controls.[48] These data argue against routine colonoscopy in patients with typical IBS symptoms and no concerning

features. Noninvasive biomarkers may provide a more cost-effective means by which to screen for inflammatory bowel disease than colonoscopy. A recent systematic review and meta-analysis suggested that fecal calprotectin, a biochemical assay for intestinal inflammation, was effective and cost-effective in identifying inflammatory bowel disease.[49] Another systematic review and meta-analysis found that a C-reactive protein level of less than 0.5 mg/dL or fecal calprotectin level of less than 40 µg/g conferred a less than 1% risk of inflammatory bowel disease in patients with typical IBS symptoms.[50]

Perfusion of bile acids into the colon stimulates water and electrolyte secretion and accelerates transit.[51] Evidence of bile acid malabsorption may be present in up to a third of patients with IBS-D symptoms.[52] At present, clinicians can assess for bile acid malabsorption by instituting an empirical trial with a bile acid sequestrant. Several tests have been developed to identify such malabsorption, including the SeHCAT (tauroselcholic [selenium 75] acid) retention test, serum C4 measurement, and fecal bile acid measurement. However, these tests are not widely available in the United States. It is hoped that eventually bile acid malabsorption testing will identify IBS-D patients more likely to benefit from a bile acid sequestrant.

For IBS-C patients, colorectal cancer is a common concern. A meta-analysis that included 8 cross-sectional surveys found that constipation was actually associated with a lower prevalence of colorectal cancer (odds ratio, 0.56; 95% CI, 0.36-0.89). This analysis also found no significant increase in colorectal cancer risk among constipated patients vs nonconstipated controls in 3 cohort studies (odds ratio, 0.80; 95% CI, 0.61-1.04).[53] However, a more recent case-control study found that patients with chronic constipation have a significantly higher prevalence and incidence of colorectal cancer and benign colorectal neoplasms.[54] The limited prospective literature suggests that the risk of colorectal cancer is less than 1% in patients

Table. Summary of Therapies for Irritable Bowel Syndrome[a]

Treatment	Quality of Evidence	Treatment Benefits	Most Common Adverse Events
Over-the-Counter			
Fiber: psyllium	Moderate	Best suited for IBS-C	Bloating, gas
Laxatives: polyethylene glycol	Very low	Beneficial for constipation but not global symptoms or pain in IBS-C	Bloating, cramping, diarrhea
Antidiarrheals: loperamide	Very low	Beneficial for diarrhea but not global symptoms or pain in IBS-D	Constipation
Probiotics	Low	Possible benefits for global symptoms, bloating, and gas as a class but unable to recommend specific probiotics	Similar to placebo
Antispasmodics: peppermint oil	Moderate	Benefits for global symptoms and cramping	GERD, constipation
Prescription			
Antidepressants: TCAs, SSRIs, SNRIs	High	TCAs and SSRIs improve global symptoms and pain; leverage adverse effects to choose TCAs for IBS-D patients and SSRIs for IBS-C patients	Dry eyes/mouth, sedation, constipation, or diarrhea
Antispasmodics	Low	Some drugs offer benefits for global symptoms and pain	Dry eyes/mouth, sedation, constipation
Prosecretory agents			
Linaclotide	High	Improves global, abdominal, and constipation symptoms in IBS-C	Diarrhea
Lubiprostone	Moderate	Improves global, abdominal, and constipation symptoms in IBS-C	Nausea, diarrhea
Antibiotics: rifaximin	Moderate	Improves global symptoms, pain, and bloating in nonconstipated IBS patients	Similar to placebo
5-HT$_3$ receptor antagonists: alosetron	Moderate	Improves global, abdominal, and diarrhea symptoms in women with severe IBS-D	Constipation, rare ischemic colitis
Other Therapies			
Psychological/behavioral therapy	Very low	Benefits for global IBS symptoms in all subgroups	Similar to placebo

Abbreviations: GERD, gastroesophageal reflux disease; IBS, irritable bowel syndrome; IBS-C, IBS with constipation; IBS-D, IBS with diarrhea; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

[a] Quality of Evidence were taken from Ford et al.[59] Quality of the evidence was reported as very low, low, moderate, or high based on the number and quality of available clinical trials and reproducibility of the results. Evidence judged to be of very low quality was from case series and nonrandomized trials while evidence judged to be of high quality was taken from randomized placebo-controlled trials with reproducible results.

with typical IBS symptoms and no concerning features and not increased compared with that in healthy controls. As such, in patients with typical IBS symptoms and no concerning features, age-appropriate colorectal cancer screening is the most logical recommendation.

An underrecognized condition in patients with IBS-C symptoms is dyssynergic defecation, a constipation-associated condition that arises from the inability to coordinate the abdominal wall, anal sphincter, and pelvic floor muscles in a way that enables normal defecation.[55] Although a sense of incomplete evacuation after a bowel movement or the need for digital maneuvers to facilitate defecation may increase the likelihood of dyssynergia, symptoms generally do not accurately identify affected patients.[56] Dyssynergia can cause abdominal symptoms such as pain, discomfort, and bloating, which are relevant to IBS-C. Preliminary data suggest that correction of dyssynergia with biofeedback can improve both bowel and abdominal symptoms.[57] Thus, patients with medically refractory IBS-C symptoms should be referred to a specialist for evaluation of dyssynergia with a digital rectal examination, anorectal manometry, balloon expulsion testing, or anorectal imaging.

Management

General Management Recommendations

A trusting patient-physician relationship is the cornerstone of managing IBS patients. Actively listening, not interrupting, using empathy, setting realistic expectations ("helping" rather than "curing"), and

using nonverbal techniques such as making eye contact, nodding, leaning forward, and using open body posture can help build this relationship.[58] The clinician must understand the patient's goals for the visit and avoid focusing only on the gastrointestinal symptoms. Performing a physical examination establishes the ritual of touch, which many patients identify with a thorough and caring physician. It is critical to assign a confident diagnosis and provide education regarding the causes, natural history, and treatment of IBS.

Because IBS is a symptom-based disorder, treatments can address abdominal symptoms such as pain, cramping, bloating, or bowel symptoms, including diarrhea and constipation (Box 2). Traditionally, first-line IBS therapies have focused on over-the-counter medications aimed at improving diarrhea (eg, loperamide, probiotics) or constipation (eg, fiber supplements, laxatives). Benefits of this strategy include improving altered bowel habits, widespread availability, low cost, and an excellent safety record. However, over-the-counter medications offer little benefit for global, or overall, IBS symptoms or abdominal symptoms such as pain and bloating. The **Table** provides a summary of commonly used IBS treatments, along with recently published recommendations and evidence quality assessments from the American College of Gastroenterology Functional Bowel Disorders Task Force.[59] During the last 5 years, lifestyle and dietary interventions have become an increasingly important first-line treatment option.

Exercise

Physically active individuals move their bowels more often and have more rapid colon transit than sedentary individuals.[60] Further-

more, a randomized clinical trial found that a structured exercise intervention led to greater improvements in overall IBS symptoms than usual care.[61] Thus, IBS patients should be encouraged to increase their physical activity. A simple recommendation is to take a 20-minute walk (roughly 1 mile) each day. Distance and pace can be gradually increased as tolerated.

Diet

Patients often associate their IBS symptoms with eating a meal. Up to 90% of IBS patients restrict their diet to prevent or improve their symptoms.[62] True food allergies are uncommon in IBS. On the other hand, food intolerances or sensitivities are frequently reported. At present, there is emerging evidence that supports diets for IBS patients that are gluten free and low in fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAP).

The effect of gluten was assessed by a randomized, double-blind, placebo-controlled, rechallenge trial in 34 IBS patients with a history of gluten sensitivity.[63] During 6 weeks, overall IBS symptoms were not adequately controlled in 68% of patients receiving gluten vs 40% receiving a gluten-free diet ($P < .001$). Gluten worsened pain, bloating, and stool consistency, as well as "tiredness." Another study in IBS-D patients reported increased stool frequency, as well as altered gut permeability and immune activation, in the presence of gluten.[64] These data have led some to conclude that gluten is the primary cause of symptoms after ingestion of wheat. However, wheat contains fructans and other proteins that might also cause symptoms in IBS patients. In a recent Australian study of 37 IBS patients with wheat sensitivity, symptom relief was more closely associated with exclusion of poorly absorbed carbohydrates than gluten.[65] It is also likely that widespread negative media reports about gluten have increased the chance of a "nocebo" response, contributing to the perceived negative effects of eating gluten-containing foods.

Short-chain, poorly absorbed, highly fermentable carbohydrates are collectively known as FODMAPs and are found in such foods as wheat, onions, some fruits and vegetables, sorbitol, and some dairy. FODMAPs lead to increased small intestinal and colonic water secretion and fermentation, which causes increased production of short-chain fatty acids and gas.[66] Aside from increased flatulence, FODMAPs do not cause gastrointestinal symptoms in healthy adults.[67] Conversely, FODMAPs are an important trigger of meal-related symptoms in IBS patients, possibly as a consequence of underlying abnormalities in gut physiology and visceral sensation.[29] A randomized clinical trial in 30 IBS patients found lower overall symptom scores on the low-FODMAP diet vs a typical Australian diet ($P < .001$).[67] Seventy percent of IBS patients felt better while receiving the low-FODMAP diet regardless of IBS subtype. Responders to full FODMAP exclusion should gradually reintroduce FODMAP-containing foods to identify the level of dietary restriction needed to maintain symptom benefit. There are currently few long-term efficacy or safety data for the low-FODMAP diet.

Given the rapidly expanding role of dietary intervention in the primary management of IBS and other gastrointestinal conditions, it is becoming increasingly important for clinicians to become educated and to integrate a trained registered dietitian into the health care team.

Medical Treatments for IBS-D

Antidiarrheals

Antidiarrheal medications such as loperamide inhibit peristalsis, prolong gut transit, reduce fecal volume, and are often used as first-line agents in patients with IBS-D. Two randomized trials enrolling IBS-D and IBS-M patients found no benefit of loperamide over placebo for overall IBS symptoms.[59] However, loperamide reduces stool frequency, increases stool consistency, and can be used prophylactically when a patient anticipates diarrhea. When used long term, loperamide is preferred to diphenoxylate or atropine because it does not cross the blood-brain barrier and thus is less subject to habituation. In practice, many gastroenterologists use bile acid sequestrants such as cholestyramine and colesevelam to treat diarrhea. These agents have not been evaluated in rigorous, randomized trials with IBS patients.

Serotonin Agents: 5-HT$_3$ Receptor Antagonists

The gut hormone serotonin influences gastrointestinal motility and visceral sensation.[68] Alosetron is a 5-HT$_3$ antagonist approved in the United States for treating women with severe, disabling IBS-D that has not responded to traditional medical therapies. Alosetron (0.5-1 mg once to twice per day) improves global and individual IBS-D symptoms in women and men for up to a year, with a therapeutic gain over placebo of approximately 15%. Dose-dependent constipation and idiosyncratic ischemic colitis are potential adverse effects of alosetron that have led to a risk management plan requiring US patients and prescribers to acknowledge the risks before dispensation of the medication.[69]

Ondansetron, a 5-HT$_3$ antagonist that is less potent than alosetron, has been shown to benefit IBS-D in a recent randomized, double-blind, placebo-controlled, crossover study.[70] Ondansetron (4-8 mg 1-3 times per day) significantly improved stool consistency, global IBS symptoms, urgency, stool frequency, and bloating (all comparisons, $P \leq .002$) but not pain.

Antispasmodics

Antispasmodics include drugs with anticholinergic or calcium-channel blocking properties that may improve IBS symptoms by relaxing gut smooth muscle. Acknowledging the poor quality of many trials, a 2011 Cochrane review reported benefits of antispasmodics over placebo for abdominal pain and global assessment.[71] The American College of Gastroenterology Functional Bowel Disorders Task Force recently concluded that "certain antispasmodics (otilonium, hyoscine, cimetropium, pinaverium, and dicyclomine) provide symptomatic short-term relief in IBS."[59] Because some IBS patients have an exaggerated gastrocolonic reflex that is in part cholinergically mediated,[72] these drugs may be best suited for postprandial abdominal cramping and loose stools. Dose-dependent adverse events, including constipation, fatigue, dry mouth, dizziness, and blurred vision, may occur. Anticholinergics should be avoided in the elderly.

Peppermint oil, which is available over the counter, possesses calcium-channel blocking properties and thus is classified as an antispasmodic. A number of small clinical trials suggest that enteric peppermint oil (187-225 mg 3 times daily) benefits some IBS patients.[73] Although peppermint oil is typically well tolerated, some patients may experience reflux symptoms.[73]

Medical Treatments for IBS-C

Fiber Supplements
The efficacy of fiber for treating IBS has been summarized in recent reviews.[26,74] The most recent meta-analysis reported modest benefits with fiber for global IBS symptoms (relative risk, 0.86; 95% CI, 0.80-0.94; number needed to treat, 10).[74] In a subgroup analysis, soluble fiber (psyllium and ispaghula husk; relative risk, 0.84; 95% CI, 0.73-0.94) but not insoluble fiber (wheat bran) was associated with improved IBS symptoms. Benefits of fiber appear most robust in patients with IBS-C rather than IBS-D. Fiber, which is often used as a first-line therapy, should be started at a nominal dose and gradually titrated upward during weeks to a total daily intake of 20 to 30 g. Wheat bran contains fructans, which, like other FODMAPs, can exacerbate IBS symptoms; thus, wheat bran should be avoided in IBS patients.[26]

Laxative Agents
Osmotic laxatives such as polyethylene glycol are frequently recommended as first-line therapy for IBS-C patients. Clinical trials have demonstrated that it improves bowel complaints, including stool frequency and consistency, but does not reliably improve abdominal pain or bloating.[75] The usual starting dose is 17 g in juice or water, with dose escalation dictated by clinical response. Polyethylene glycol is typically well tolerated but can cause dose-dependent bloating, gas, and loose stools.

Stimulant laxatives are also commonly used in IBS-C patients. Although efficacy has been demonstrated in patients with chronic constipation,[76] to our knowledge there are no randomized, controlled trials in IBS-C patients. Relevant to IBS, the most common adverse effects are abdominal pain and cramping.

Prosecretory Agents
Luminally acting prosecretory agents have been evaluated in IBS-C patients. Lubiprostone is a chloride-channel (ClC-2) activator that stimulates intestinal fluid secretion and improves global, bowel, and abdominal symptoms in IBS-C patients.[77] In 2 phase 3 trials (1711 IBS-C patients), a significantly higher percentage of patients treated with lubiprostone 8 µg twice daily responded compared with those treated with placebo (17.9% vs 10.1%; P = .001).[78] A higher dosage of 24 µg has proven effective in patients with chronic idiopathic constipation. To limit dose-dependent nausea (8% with an 8-µg dose and 33% with a 24-µg dose), lubiprostone should be received with food.

Linaclotide is a guanylate cyclase-C agonist that increases production of cyclic guanosine monophosphate. Intracellularly, cyclic guanosine monophosphate increases intestinal chloride secretion via the cystic fibrosis transmembrane regulator, whereas extracellularly it reduces firing of visceral afferent pain fibers.[79] A 2013 meta-analysis that included 3 rigorous randomized clinical trials in IBS-C patients reported a relative risk for response to linaclotide (290 µg once daily) vs placebo of 1.95 (95% CI, 1.3-2.9) and a number needed to treat of 7 (95% CI, 5-11).[80] The maximum benefit for stool frequency occurs within a week of treatment initiation, whereas abdominal pain and bloating may take 8 to 12 weeks to maximally improve. Diarrhea is the most common adverse effect with linaclotide, reported by 20% of patients.[81] Linaclotide should be received 30 to 60 minutes before breakfast to reduce the likelihood of diarrhea.

Modification of the Microbiota: Probiotics and Antibiotics
Probiotics are live bacteria that, when consumed in sufficient quantities, confer a health benefit to the host. Prebiotics are nutrients, usually carbohydrates, that encourage the growth of probiotic bacteria. Synbiotics are combinations of prebiotics and probiotics. Postbiotics consist of extracts from dead or lysed bacteria. The most robust data have evaluated the role of probiotics for IBS. In a recent meta-analysis including 35 randomized clinical trials, probiotics as a group improved global IBS symptoms (relative risk, 0.79; 95% CI, 0.70-0.89; number needed to treat, 7; 95% CI, 4-12.5), abdominal pain, bloating, and flatulence.[59] However, given the differences in probiotic preparations evaluated, data derived from grouping or directly comparing trials should be interpreted with caution.[82] Higher-quality studies have tended to demonstrate less of a treatment effect. Thus, the current literature does not allow recommendations regarding specific probiotic preparations for IBS.

Rifaximin is a poorly absorbed, broad-spectrum antibiotic that has been evaluated in IBS patients. A recent meta-analysis that included 5 randomized clinical trials that enrolled predominantly nonconstipated IBS patients demonstrated therapeutic gains of 9% to 10% for global symptoms (odds ratio, 1.57; 95% CI, 1.22-2.01) and bloating (odds ratio, 1.55; 95% CI, 1.23-1.96).[83] The 2 phase 3 trials in nonconstipated IBS patients used rifaximin 550 mg 3 times daily for 14 days. Clinical experience suggests that many rifaximin responders will eventually develop recurrent IBS symptoms. Recently released data from a large re-treatment trial suggest that second and third courses yield efficacy similar to that of the first course of rifaximin.[84] The role of other antibiotics in IBS treatment remains unknown, although antimicrobial resistance with repeated courses of systemically absorbed antibiotics may be a concern.

Centrally Acting Interventions

Antidepressants
Because of their effects on pain perception, mood, and motility, antidepressants have become a widespread treatment option for patients with moderate to severe IBS. The efficacy of tricyclic antidepressants, selective serotonin-reuptake inhibitors, and, to a lesser extent, selective norepinephrine-reuptake inhibitors has been evaluated in IBS patients.[85] A meta-analysis identified 17 randomized controlled trials that enrolled 1084 IBS patients who were treated with antidepressants or placebo.[85] Collectively, antidepressants were effective for abdominal pain, with a relative risk of remaining symptomatic of 0.62 (95% CI, 0.43-0.88) and a number needed to treat of 4 (95% CI, 3-6). A subgroup analysis reported a number needed to treat of 4 for both tricyclic antidepressants and selective serotonin-reuptake inhibitors. Adverse events occurred more often in patients receiving an antidepressant (number needed to harm, 9; 95% CI, 5-111). Tricyclic antidepressants can cause dose-dependent constipation, dry mouth and eyes, drowsiness, weight gain, and QT-interval prolongation. Selective serotonin-reuptake inhibitors can cause sexual dysfunction, agitation, nausea, drowsiness, and diarrhea. Although selective norepinephrine-reuptake inhibitors offer benefits for anxiety, depression, and somatic pain, there are few data addressing their efficacy for IBS.[86]

The adverse event profiles of different antidepressants can be leveraged to address different IBS subtypes.[87] For example, because tricyclic antidepressants can cause constipation, they may be best suited to IBS-D patients, whereas the prokinetic effects of se-

lective serotonin-reuptake inhibitors might make them a better choice for IBS-C patients. Similarly, tricyclic antidepressants might be a better choice for patients with insomnia, anorexia, or weight loss. On the other hand, selective serotonin-reuptake inhibitors might be a better choice for patients with significant anxiety. When a tricyclic antidepressant is selected to treat IBS, low doses (10-25 mg) should be started at bedtime and gradually titrated upward according to symptom response and tolerability. Selective serotonin-reuptake inhibitors are typically started at the lower range of standard dosing.

Psychological Therapies

Psychological therapies provide an alternative or adjunctive therapy for IBS patients. In a recent meta-analysis, 32 separate trials of highly variable quality, involving more than 2000 patients, evaluated 10 different "psychological therapies,"[85] which were more effective than control therapies, with a number needed to treat of 4 (95% CI, 3-5). In a subgroup analysis, similar numbers needed to treat were reported for cognitive behavioral therapy, hypnotherapy, multicomponent psychotherapy, and dynamic psychotherapy but not other techniques. Despite these encouraging results, variable third-party reimbursement, a lack of clinicians, and poor patient and clinician acceptance have limited widespread adoption of these therapies in clinical practice. Access to behavioral therapy may improve with the development of book-, Internet-, or application-based behavioral programs.[88,89]

Complementary and Alternative Medicine

Despite the paucity of evidence, many IBS patients use complementary and alternative therapies.[90] A meta-analysis of 5 studies demonstrated that acupuncture was no better than sham acupuncture in improving symptoms or quality of life in IBS patients.[91] Studies evaluating Chinese herbal remedies for IBS have yielded mixed results.[90] A clear understanding of the active ingredients and a lack of standardization are significant challenges facing clinicians with an interest in herbal therapies.

Bottom-Line Clinical Messages

1. IBS is a common, symptom-based illness that is defined by the presence of abdominal pain or cramping in association with constipation, diarrhea, or both.
2. The diagnosis of IBS can be confidently established with the use of symptom-based criteria, the exclusion of concerning features, and the judicious use of diagnostic testing.
3. Concerning features that should prompt a more detailed evaluation include new onset of symptoms after age 50 years; unexplained weight loss; a family history of organic gastrointestinal diseases such as colon cancer, inflammatory bowel diseases, or celiac disease; gastrointestinal blood loss; and unexplained iron-deficiency anemia.
4. Successful management of patients with IBS begins with a trusting, positive, patient-physician relationship.
5. A holistic approach that embraces lifestyle changes, dietary interventions, medications, or behavioral strategies offers the greatest likelihood of sustained treatment benefit.

Conclusions

IBS remains an enigmatic cause of significant distress, morbidity, and disability. For the foreseeable future, the diagnosis of IBS will rely on the identification of characteristic symptoms and the exclusion of organic disease mimics. As science advances, it is hoped that the confident diagnosis of IBS will be aided by novel biomarkers that can either rule out specific organic diseases or rule in IBS. An improved understanding of the pathophysiology of IBS will also pave the way for novel nonpharmacologic and pharmacologic therapies. For now, it is important for physicians to understand the role of dietary, lifestyle, and behavioral modification either with or without medical treatments for IBS.

REFERENCES

1. 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.

2. 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.

3. Guilera M, Balboa A, Mearin F. Bowel habit subtypes and temporal patterns in irritable bowel syndrome: systematic review. *Am J Gastroenterol*. 2005;100(5):1174-1184.

4. 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.

5. Lovell RM, Ford AC. Prevalence of gastro-esophageal reflux-type symptoms in individuals with irritable bowel syndrome in the community: a meta-analysis. *Am J Gastroenterol*. 2012;107(12):1793-1801.

6. Ford AC, Marwaha A, Lim A, Moayyedi P. Systematic review and meta-analysis of the prevalence of irritable bowel syndrome in individuals with dyspepsia. *Clin Gastroenterol Hepatol*. 2010;8(5):401-409.

7. 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.

8. El-Serag HB, Pilgrim P, Schoenfeld P. Systemic review: natural history of irritable bowel syndrome. *Aliment Pharmacol Ther*. 2004;19(8):861-870.

9. 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.

10. Garrigues V, Mearin F, Badía X, et al; RITMO GROUP. Change over time of bowel habit in irritable bowel syndrome: a prospective, observational, 1-year follow-up study (RITMO study). *Aliment Pharmacol Ther*. 2007;25(3):323-332.

11. Spiegel BM. The burden of IBS: looking at metrics. *Curr Gastroenterol Rep*. 2009;11(4):265-269.

12. Koloski NA, Talley NJ, Boyce PM. Predictors of health care seeking for irritable bowel syndrome and nonulcer dyspepsia: a critical review of the literature on symptom and psychosocial factors. *Am J Gastroenterol*. 2001;96(5):1340-1349.

13. Everhart JE, Ruhl CE. Burden of digestive diseases in the United States, part II: lower gastrointestinal diseases. *Gastroenterology*. 2009; 136(3):741-754.

14. Agarwal N, Spiegel BM. The effect of irritable bowel syndrome on health-related quality of life and health care expenditures. *Gastroenterol Clin North Am*. 2011;40(1):11-19.

15. Simrén M, Barbara G, Flint HJ, et al; Rome Foundation Committee. Intestinal microbiota in functional bowel disorders: a Rome Foundation report. *Gut*. 2013;62(1):159-176.

16. Dupont HL. Review article: evidence for the role of gut microbiota in irritable bowel syndrome and its potential influence on therapeutic targets. *Aliment Pharmacol Ther*. 2014;39(10):1033-1042.

17. Sainsbury A, Sanders DS, Ford AC. Prevalence of irritable bowel syndrome–type symptoms in patients with celiac disease: a meta-analysis. *Clin Gastroenterol Hepatol*. 2013;11(4):359-365.e1.

18. Halpin SJ, Ford AC. Prevalence of symptoms meeting criteria for irritable bowel syndrome in inflammatory bowel disease: systematic review and meta-analysis. *Am J Gastroenterol*. 2012;107(10): 1474-1482.

19. Dai C, Jiang M. The incidence and risk factors of post-infectious irritable bowel syndrome: a meta-analysis. *Hepatogastroenterology*. 2012;59 (113):67-72.

20. Öhman L, Simrén M. Pathogenesis of IBS: role of inflammation, immunity and neuroimmune interactions. *Nat Rev Gastroenterol Hepatol*. 2010;7 (3):163-173.

21. Ford AC, Talley NJ. Mucosal inflammation as a potential etiological factor in irritable bowel syndrome: a systematic review. *J Gastroenterol*. 2011;46(4):421-431.

22. Matricon J, Meleine M, Gelot A, et al. Review article: associations between immune activation, intestinal permeability and the irritable bowel syndrome. *Aliment Pharmacol Ther*. 2012;36(11-12): 1009-1031.

23. Zhou Q, Zhang B, Verne GN. Intestinal membrane permeability and hypersensitivity in the irritable bowel syndrome. *Pain*. 2009;146(1-2):41-46.

24. Collins SM. A role for the gut microbiota in IBS. *Nat Rev Gastroenterol Hepatol*. 2014;11(8):497-505.

25. 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.

26. Eswaran S, Muir J, Chey WD. Fiber and functional gastrointestinal disorders. *Am J Gastroenterol*. 2013;108(5):718-727.

27. Boettcher E, Crowe SE. Dietary proteins and functional gastrointestinal disorders. *Am J Gastroenterol*. 2013;108(5):728-736.

28. Farré R, Tack J. Food and symptom generation in functional gastrointestinal disorders: physiological aspects. *Am J Gastroenterol*. 2013;108 (5):698-706.

29. Shepherd SJ, Lomer MC, Gibson PR. Short-chain carbohydrates and functional gastrointestinal disorders. *Am J Gastroenterol*. 2013;108(5):707-717.

30. Park MI, Camilleri M. Is there a role of food allergy in irritable bowel syndrome and functional dyspepsia? a systematic review. *Neurogastroenterol Motil*. 2006;18(8):595-607.

31. Drossman DA. Abuse, trauma, and GI illness: is there a link? *Am J Gastroenterol*. 2011;106(1):14-25.

32. Chitkara DK, van Tilburg MA, Blois-Martin N, Whitehead WE. Early life risk factors that contribute to irritable bowel syndrome in adults: a systematic review. *Am J Gastroenterol*. 2008;103(3):765-774.

33. Mayer EA, Tillisch K. The brain-gut axis in abdominal pain syndromes. *Annu Rev Med*. 2011; 62:381-396.

34. 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.

35. Keefer L, Mandal S. The potential role of behavioral therapies in the management of centrally mediated abdominal pain. *Neurogastroenterol Motil*. doi: 10.1111/nmo.12474.

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

37. Saad RJ, Rao SS, Koch KL, et al. Do stool form and frequency correlate with whole-gut and colonic transit? results from a multicenter study in constipated individuals and healthy controls. *Am J Gastroenterol*. 2010;105(2):403-411.

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

39. Ringel Y, Williams RE, Kalilani L, Cook SF. Prevalence, characteristics, and impact of bloating symptoms in patients with irritable bowel syndrome. *Clin Gastroenterol Hepatol*. 2009;7(1): 68-72.

40. Tuteja AK, Talley NJ, Joos SK, Tolman KG, Hickam DH. Abdominal bloating in employed adults: prevalence, risk factors, and association with other bowel disorders. *Am J Gastroenterol*. 2008;103(5):1241-1248.

41. Brandt LJ, Chey WD, Foxx-Orenstein AE, et al; American College of Gastroenterology Task Force on Irritable Bowel Syndrome. An evidence-based position statement on the management of irritable bowel syndrome. *Am J Gastroenterol*. 2009;104 (suppl 1):S1-S35.

42. Vanner SJ, Depew WT, Paterson WG, et al. Predictive value of the Rome criteria for diagnosing the irritable bowel syndrome. *Am J Gastroenterol*. 1999;94(10):2912-2917.

43. 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.

44. Ford AC, Chey WD, Talley NJ, Malhotra A, Spiegel BM, Moayyedi P. Yield of diagnostic tests for celiac disease in individuals with symptoms suggestive of irritable bowel syndrome: systematic review and meta-analysis. *Arch Intern Med*. 2009; 169(7):651-658.

45. Cash BD, Rubenstein JH, Young PE, et al. The prevalence of celiac disease among patients with nonconstipated irritable bowel syndrome is similar to controls. *Gastroenterology*. 2011;141(4):1187-1193.

46. Spiegel BM, DeRosa VP, Gralnek IM, Wang V, Dulai GS. Testing for celiac sprue in irritable bowel syndrome with predominant diarrhea: a cost-effectiveness analysis. *Gastroenterology*. 2004;126(7):1721-1732.

47. Macaigne G, Lahmek P, Locher C, et al. Microscopic colitis or functional bowel disease with diarrhea: a French prospective multicenter study. *Am J Gastroenterol*. 2014;109(9):1461-1470.

48. Chey WD, Nojkov B, Rubenstein JH, Dobhan RR, Greenson JK, Cash BD. 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.

49. Yang Z, Clark N, Park KT. Effectiveness and cost-effectiveness of measuring fecal calprotectin in diagnosis of inflammatory bowel disease in adults and children. *Clin Gastroenterol Hepatol*. 2014;12(2):253-262.e2.

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

51. Shin A, Camilleri M, Vijayvargiya P, et al. Bowel functions, fecal unconjugated primary and secondary bile acids, and colonic transit in patients with irritable bowel syndrome. *Clin Gastroenterol Hepatol*. 2013;11(10):1270-1275.e1.

52. 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.

53. Power AM, Talley NJ, Ford AC. Association between constipation and colorectal cancer: systematic review and meta-analysis of observational studies. *Am J Gastroenterol*. 2013;108 (6):894-903.

54. Guérin A, Mody R, Fok B, et al. Risk of developing colorectal cancer and benign colorectal neoplasm in patients with chronic constipation. *Aliment Pharmacol Ther*. 2014;40(1):83-92.

55. Wald A, Bharucha AE, Cosman BC, Whitehead WE. ACG clinical guideline: management of benign anorectal disorders. *Am J Gastroenterol*. 2014;109(8):1141-1157, quiz 1058.

56. 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.e2.

57. 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.

58. Drossman DA. 2012 David Sun lecture: helping your patient by helping yourself—how to improve the patient-physician relationship by optimizing communication skills. *Am J Gastroenterol*. 2013;108 (4):521-528.

59. Ford AC, Moayyedi P, Lacy BE, et al; Task Force on the Management of Functional Bowel Disorders. 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.

60. Song BK, Cho KO, Jo Y, Oh JW, Kim YS. Colon transit time according to physical activity level in adults. *J Neurogastroenterol Motil*. 2012;18(1):64-69.

61. 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.

62. 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.

63. 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.

64. 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.e3.

65. 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.e1-3.

66. 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.

67. 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.e5.

68. Mawe GM, Hoffman JM. Serotonin signalling in the gut--functions, dysfunctions and therapeutic targets. *Nat Rev Gastroenterol Hepatol*. 2013;10(8): 473-486.

69. Chang L, Chey WD, Harris L, Olden K, Surawicz C, Schoenfeld P. Incidence of ischemic colitis and serious complications of constipation among patients using alosetron: systematic review of clinical trials and post-marketing surveillance data. *Am J Gastroenterol*. 2006;101(5):1069-1079.

70. Garsed K, Chernova J, Hastings M, et al. A randomised trial of ondansetron for the treatment of irritable bowel syndrome with diarrhoea. *Gut*. 2014;63(10):1617-1625.

71. Ruepert L, Quartero AO, de Wit NJ, van der Heijden GJ, Rubin G, Muris JW. Bulking agents, antispasmodics and antidepressants for the treatment of irritable bowel syndrome. *Cochrane Database Syst Rev*. 2011;(8):CD003460.

72. Chey WY, Jin HO, Lee MH, Sun SW, Lee KY. Colonic motility abnormality in patients with irritable bowel syndrome exhibiting abdominal pain and diarrhea. *Am J Gastroenterol*. 2001;96(5):1499-1506.

73. Khanna R, MacDonald JK, Levesque BG. Peppermint oil for the treatment of irritable bowel syndrome: a systematic review and meta-analysis. *J Clin Gastroenterol*. 2014;48(6):505-512.

74. Moayyedi P, Quigley EM, Lacy BE, et al. The effect of fiber supplementation on irritable bowel syndrome: a systematic review and meta-analysis. *Am J Gastroenterol*. 2014;109(9):1367-1374.

75. 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.

76. Kamm MA, Mueller-Lissner S, Wald A, Richter E, Swallow R, Gessner U. Oral bisacodyl is effective and well-tolerated in patients with chronic constipation. *Clin Gastroenterol Hepatol*. 2011;9(7): 577-583.

77. Lacy BE, Chey WD. Lubiprostone: chronic constipation and irritable bowel syndrome with constipation. *Expert Opin Pharmacother*. 2009;10 (1):143-152.

78. Drossman DA, Chey WD, Johanson JF, et al. Clinical trial: lubiprostone in patients with constipation-associated irritable bowel syndrome—results of two randomized, placebo-controlled studies. *Aliment Pharmacol Ther*. 2009;29(3):329-341.

79. Castro J, Harrington AM, Hughes PA, et al. Linaclotide inhibits colonic nociceptors and relieves abdominal pain via guanylate cyclase-C and extracellular cyclic guanosine 3',5'-monophosphate. *Gastroenterology*. 2013;145(6):1334-1346.

80. Videlock EJ, Cheng V, Cremonini F. Effects of linaclotide in patients with irritable bowel syndrome with constipation or chronic constipation: a meta-analysis. *Clin Gastroenterol Hepatol*. 2013;11(9):1084-1092.e3.

81. Chey WD, Lembo AJ, Lavins BJ, et al. Linaclotide for irritable bowel syndrome with constipation: a 26-week, randomized, double-blind, placebo-controlled trial to evaluate efficacy and safety. *Am J Gastroenterol*. 2012;107(11):1702-1712.

82. Brenner DM, Moeller MJ, Chey WD, Schoenfeld PS. The utility of probiotics in the treatment of irritable bowel syndrome: a systematic review. *Am J Gastroenterol*. 2009;104(4):1033-1049.

83. Menees S, Maneerattanaporn M, Chey W. Efficacy of rifaximin in patients with irritable bowel syndrome: a meta-analysis. *Am J Gastroenterol*. 2012;107(5):28-35.

84. Salix Pharmaceuticals Inc. Salix's TARGET 3 study examines the safety and efficacy of repeat treatment with rifaximin 550 mg for irritable bowel syndrome with diarrhea. http://news.salix.com /press-release/salixs-target-3-study-examines -safety-and-efficacy-repeat-treatment-rifaximin -550-mg. Accessed January 25, 2015.

85. 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.

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

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

88. Hunt MG, Moshier S, Milonova M. Brief cognitive-behavioral internet therapy for irritable bowel syndrome. *Behav Res Ther*. 2009;47(9):797-802.

89. 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.

90. Hussain Z, Quigley EM. Systematic review: complementary and alternative medicine in the irritable bowel syndrome. *Aliment Pharmacol Ther*. 2006;23(4):465-471.

91. Manheimer E, Wieland LS, Cheng K, et al. Acupuncture for irritable bowel syndrome: systematic review and meta-analysis. *Am J Gastroenterol*. 2012;107(6):835-847.