REPORT

Evidence-Based Management of Irritable Bowel Syndrome With Diarrhea

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ABSTRACT

Irritable bowel syndrome (IBS), a complex disorder of the gastrointestinal tract, is characterized by abdominal pain associated with defecation or changes in stool form or frequency. IBS is associated with substantial burden, including direct medical costs and indirect costs. Direct costs associated with IBS in the United States have been estimated to exceed $1 billion. However, indirect costs, such as negative effect on quality of life (QOL) and work productivity, are difficult to quantify. There are 3 main subtypes: IBS with prominent diarrhea (IBS-D), IBS with constipation, and IBS with mixed symptoms of both constipation and diarrhea. A number of pharmacologic agents have been used to treat IBS-D despite lack of approval by the FDA for this indication. The pharmacologic agents that are indicated by the FDA for the treatment of IBS-D include alosetron, eluxadoline, and rifaximin. The negative impact of IBS-D symptoms on QOL reported by patients indicate there is an unmet need for therapies that effectively treat and manage the symptoms of this condition. Addressing gaps in treatment is an important priority.

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For author information and disclosures, see end of text.

Irritable bowel syndrome (IBS) is a chronic, potentially disabling disorder of the gastrointestinal (GI) tract with a relapsing/remitting course in which abdominal pain is associated with defecation or changes in stool form or frequency.[1-3]

Diagnosis of IBS

The Rome IV criteria represent the current standard for diagnosing IBS. In 2016, the Rome III criteria were updated by a group of multinational experts in functional GI disorders.[2,3] The most significant change from the Rome III criteria is the elimination of the term "discomfort" from the definition, as it is vague.[3]

The current diagnostic criteria for IBS include abdominal pain at least 1 day per week during the last 3 months that is associated with at least 2 of the following[3]:

- Defecation
- Change in stool frequency
- Change in stool form (ie, appearance)

To receive a diagnosis of IBS, individuals must have symptoms meeting the diagnostic criteria for 3 months, with the onset of initial symptoms at least 6 months before diagnosis.[3]

The diagnosis of IBS should be based on a clinical evaluation of the patient, a physical examination, and laboratory tests (minimal) and, when clinically indicated, a colonoscopy or other appropriate tests.[3] The clinical evaluation includes determining the presence of abdominal pain, assessing bowel and dietary habits, and the patient's medical and surgical history.[2,3]

The presence of abdominal pain is required for a diagnosis of IBS. Pain usually occurs in the lower abdomen but can occur anywhere in the abdomen.[3] The presence of disordered bowel habits is also required for a diagnosis of IBS.[2] Disordered bowel habits include a history of constipation and/or diarrhea. The association of constipation and/or diarrhea with abdominal pain should be determined.[3] Abdominal bloating is not required for a diagnosis of IBS but is often present and can support the diagnosis.[2]

Physical examination in patients with IBS usually reveals abdominal tenderness but rarely other abnormalities. Physical

examination should include a digital rectal examination, particularly in patients with constipation. The presence of enlarged liver, spleen, or lymph nodes; ascites; or a mass suggests a condition other than IBS.[2] A normal physical examination and the absence of warning signs (see Differential Diagnosis section below) in the patient's history support using the Rome IV diagnostic criteria to confirm a diagnosis of IBS.[2]

Patients with IBS generally experience symptoms for extended periods before they receive a diagnosis. Individuals who have not yet been given a diagnosis of IBS may have an even greater burden of symptoms than those who have received a definitive diagnosis.[4] There are several reasons for a delayed diagnosis of IBS. Not all individuals with IBS symptoms consult a physician about their symptoms; in the United States, 30% of individuals with symptoms of IBS do so, and of these, 80% have IBS with prominent diarrhea (IBS-D). Those who see a physician have symptoms similar to those who do not but have higher pain scores, more anxiety, and poorer quality of life (QOL).[5]

Although the Rome guidelines clearly define IBS, 72% of community providers (community nonexpert gastroenterologists, general internal medicine physicians, and nurse practitioners) consider IBS a diagnosis of exclusion, whereas just 8% of experts (IBS key opinion leaders) do. This shows a clear disconnect between academic guidelines and community practice. Those who believe IBS is a diagnosis of exclusion are more likely to order additional diagnostic tests than those who do not.[6]

Classification of IBS

IBS is classified into subtypes based on symptoms. Although subtyping is used to suggest treatment, it is thought that each subtype may include more than 1 disease entity, explaining the variable responses to treatment.[2] The diagnostic criteria used to define the IBS subtypes are the predominant bowel habits based on stool form on days with at least 1 abnormal bowel movement.[3]

The Bristol Stool Form Scale (BSFS) is used to record stool consistency on days when patients are experiencing abnormal bowel habits and defines the following 7 types[3]:

Type 1: separate hard lumps, like nuts; hard to pass
Type 2: sausage-shaped but lumpy
Type 3: like a sausage but with cracks on 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: watery, no solid pieces, entirely liquid

To accurately classify the subtype of IBS based on bowel habit abnormalities using the BSFS, patients should not be taking any medications to treat their symptoms, including laxatives or antidiarrheal agents, during the period of evaluation. IBS subtyping is most accurate when patients experience abnormal bowel habits at least 4 days per month.[3]

The IBS subtypes comprise 3 classifications based on the predominant bowel disorder and include IBS-D, IBS with constipation (IBS-C), and IBS with mixed symptoms of constipation and diarrhea (IBS-M).[3] Individuals with a diagnosis of IBS whose bowel habits cannot be classified as IBS-D, IBS-C, or IBS-M are considered to have unclassified IBS (IBS-U).[3] Frequent changes in diet or medications or the inability to discontinue GI medications may interfere with accurate determination of IBS subtype.[3]

The IBS-D subtype is defined as follows: More than 25% of bowel movements using the BSFS are type 6 or 7, and less than 25% of bowel movements are type 1 or 2. Alternatively, for epidemiologic studies and in clinical practice, if the patient reports abnormal bowel movements that are usually diarrhea, the patient can be considered to have IBS-D.[3] Experiencing bowel patterns with at least 3 different types of stool in a week also supports a diagnosis of IBS-D.[3]

The IBS-C subtype is defined as follows: More than 25% of bowel movements are type 1 or 2 using the BSFS, and less than 25% are type 6 or 7. Alternatively, for epidemiologic studies and in clinical practice, if the patient reports abnormal bowel movements that are usually constipated, the patient can be considered to have IBS-C.[3]

The IBS-M subtype is defined as follows: More than 25% of bowel movements using the BSFS are types 1 and 2, and more than 25% are types 6 and 7. Alternatively, for epidemiologic studies and in clinical practice, if the patient reports abnormal bowel movements that are usually both constipation and diarrhea, the patient can be considered to have IBS-M.[3]

Patients who have the IBS-U subtype meet the diagnostic requirement for IBS, but their bowel habits cannot be accurately categorized as IBS-D, IBS-C, or IBS-M.[3]

Differential Diagnosis

IBS is not a diagnosis of exclusion.[2] However, IBS shares symptoms with other conditions that should be ruled out during diagnosis. Warning signs that suggest a diagnosis of a condition other than IBS are also known as "alarm" features or red flag symptoms. Alarm features include fever; weight loss; waking during the night as a result of GI symptoms; blood in the stool (including occult blood); family history of colon cancer or inflammatory bowel disease (IBD); recent use of antibiotics; newly onset, progressive symptoms; and onset of symptoms after age 50 years.[7]

A limited number of laboratory tests may be conducted to identify conditions other than IBS in patients,[3] including a complete blood count. Thyroid tests may be appropriate for some patients.[3] Stool tests for bacteria and parasites or their eggs may be warranted in areas where infectious causes of diarrhea are common.[3]

Bacteria that cause acute gastroenteritis, a known precipitant of IBS-D, produce cytolethal distending toxin B (CdtB). Circulating

antibodies to CdtB (anti-CdtB) also cross-react with the intestinal protein vinculin. Titers of anti-CdtB and anti-vinculin are elevated in individuals with IBS-D compared with healthy individuals or those with celiac disease and can therefore be used as biomarkers for IBS-D.[8] Celiac disease can also be distinguished via other serologic tests and confirmational duodenal biopsy.[3]

Serum C-reactive protein and fecal calprotectin can be used to rule out IBD in patients with typical IBS symptoms. However, the erythrocyte sedimentation rate and fecal lactoferrin are not useful for ruling out IBD in patients with IBS.[9]

Screening colonoscopy is warranted in patients 50 years or older, African Americans 45 years and older, patients who have a family history of colorectal cancer, those with persistent diarrhea that has not responded to empiric therapy, and those with alarm signs of other disorders.[2] These recommendations are identical to the national recommendations for the general population.[2]

Epidemiology of IBS

In a meta-analysis of 10 studies (N = 52,790), the pooled prevalence of IBS in the United States was estimated to be 11.8% (95% CI, 7.4%-17.2%).[1] IBS is reported more frequently in women than in men and in individuals aged 30 to 49 years compared with those 50 years and older.[1] In another meta-analysis of 14 studies of patients with IBS, the prevalence of IBS-D was highest, accounting for 40.0% of the patient population (95% CI, 31.0%-48.0%); the prevalence of IBS-C was 35.0% (95% CI, 29.0%-41.0%); and the prevalence of IBS-M was 23.0% (95% CI, 15.0%-31.0%).[1]

Pathophysiology of IBS

IBS is a complex disorder with a pathophysiology[3] that is not completely understood.[10] Risk factors for IBS in susceptible individuals include a genetic predisposition to the condition, exposure to environmental factors, and psychosocial factors (eg, an abnormal stress response).[3]

The onset or exacerbation of IBS symptoms can be caused by previous gastroenteritis, food intolerances, chronic stress, diverticulitis, or surgery.[3]

IBS symptoms may be caused by altered intestinal permeability resulting from infections, inflammation, or changes in the gut microbiome, all of which can trigger a release of inflammatory mediators such as cytokines or chemokines. These inflammatory mediators could lead to changes in the central nervous system that result in new onset of anxiety and depression; this, in turn, can further exacerbate IBS symptoms in a feedback loop.[2] About half of IBS cases originate in the gut rather than the brain, and psychological stress develops after IBS symptoms.[2]

IBS-like symptoms are known to persist in 10% to 20% of individuals who have had acute bacterial, protozoan, or viral gastroenteritis and can be associated with intestinal inflammation. More than 30% of individuals who have experienced gastroenteritis develop IBS-D, which is referred to as postinfectious IBS (PI-IBS).[10] The pathophysiology of PI-IBS is thought to be different from that resulting from other causes.[2] Viral gastroenteritis is less apt to lead to PI-IBS than bacterial enteritis or protozoan or helminthic infections.[11]

Clinical Burden and QOL Associated With IBS

Individuals with IBS have a lower health-related QOL compared with the US general population.[12,13] Recall that for patients to meet the diagnostic criteria of IBS, they have to have experienced symptoms for at least 6 months, thereby adding to the burden of disease.[3] Despite the effect of IBS on QOL, the burden of IBS still may be underestimated because it is not life-threatening and is not associated with a decreased life expectancy.[14]

Individuals who have been diagnosed with IBS are more likely to report that GI symptoms affect their QOL than those who have not yet received a diagnosis; nevertheless, many individuals experiencing IBS-related symptoms remain untreated.[4] Patients with IBS-D and IBS-M have a lower QOL than those with IBS-C.[14] Areas in which patients with IBS experience statistically poorer health-related QOL than the US general population include increased fatigue, role limitations, and pain.[12]

Patients with IBS have significantly lower scores for physical functioning, physical role limitations, bodily pain, emotional well-being, emotional role limitations, energy/fatigue, social functioning, and general health than the US general population.[12] For many of these QOL measures, patients with IBS also show more impairment than patients with other chronic diseases, such as gastroesophageal reflux disease, diabetes, depression, or end-stage renal disease.[12]

The domains of pain/discomfort and depression/anxiety were reported by patients with IBS as contributing to the greatest loss of QOL.[15] Although referral of patients with probable IBS to a gastroenterologist resulted in a nonsignificant increase in QOL at 3 months, this improvement was not maintained upon repeated survey at 1 year.[15]

Individuals with IBS who have lower QOL and higher levels of anxiety are more likely to have other functional comorbidities.[5] Patients with IBS and comorbidities experience more severe symptom burdens than those with IBS alone. Approximately half of all patients with IBS experience coexisting functional conditions, including fibromyalgia, chronic fatigue syndrome, chronic headache, and chronic back pain, with an incidence nearly twice that of those without IBS.[5]

IBS is also responsible for lost productivity at work,[14] including increased work absenteeism (ie, percentage of work time missed due to health problems). A UK-based study reported that those with IBS are twice as likely to miss work compared with healthy coworkers, and in the United States, those with IBS miss an average of 3 to 4 more days of work annually compared with healthy coworkers. The severity of IBS symptoms is significantly associated with the

TABLE 1. Nonpharmacologic Interventions for IBS[2]

Therapy	Quality of Evidence	Adverse Effects
Soluble fiber	Moderate	Diarrhea, constipation, bloating, flatulence
Peppermint oil	Moderate	Heartburn, dyspepsia, headache, dry mouth
Probiotics	Low	Individual adverse effects poorly reported in randomized controlled trials
Psychological therapies	Low	Individual adverse effects poorly reported in randomized controlled trials
Low-FODMAP diet	Very low	May affect colonic microbiome; long-term effects unknown
Gluten-free diet	Very low	May affect colonic microbiome; long-term effects unknown

FODMAP indicates fermentable oligosaccharides, disaccharides, monosaccharides, and polyols; IBS, irritable bowel syndrome.

need to take time off work (P <.05); an average of 1 day per month is missed in those with severe IBS symptoms.[16]

IBS symptoms are also associated with work presenteeism (ie, working but at reduced capacity or competence). Presenteeism is more subjective than absenteeism, so estimated time lost to the former varies widely, from 2% to 32%. Like absenteeism, presenteeism significantly increases with IBS symptom severity (P <.001).[16]

In a survey study of 66,491 adults in the United States,[17] patients with IBS-D had statistically significantly more work absenteeism than controls (5.1% vs 2.9%, respectively; P = .004), more presenteeism (17.9% vs 11.3%; P <.001), and greater overall work productivity loss (ie, absenteeism + presenteeism) (20.7% vs 13.2%; P <.001). In this study, patients with IBS-D also missed significantly more work days each year compared with controls (10.1 d/y vs 6.2 d/y; P = .031).[17]

In addition to interfering with work, IBS interferes with daily activities and personal and social relationships.[14] Patients with IBS-D have a significantly higher degree of daily activity impairment than controls (29.6% vs 18.9%; P <.001).[17] The partner burden with IBS was higher than that for partners of healthy individuals and comparable with that for other diseases, such as dementia. Partner burden with IBS was higher than that for caregivers of patients with terminal cancer. This burden rose with increasing severity of IBS and poorer sexual and relationship satisfaction.[18]

Approaches to Treatment of IBS-D

IBS is a symptom-based disorder. Therefore, treatments address the symptom of abdominal pain and the bowel symptoms of diarrhea and constipation. Treatment of IBS should include nonpharmacologic management, such as lifestyle and dietary interventions, and pharmacologic agents[19] and should be based on the nature and severity of the predominant symptoms (eg, abdominal pain and diarrhea).[20]

Treatments should be individualized for patients in a stepwise manner according to symptoms. Therapy comprising a low-FODMAP (fermentable oligosaccharides, disaccharides, monosaccharides, and polyols) diet, more exercise, stress reduction, and antispasmodics or tricyclic antidepressants for pain should be sustained for 1 month before discontinuation due to lack of efficacy. For patients with diarrhea, loperamide or a bile acid sequestrant can also be given. If diarrhea persists, treatment with alosetron, eluxadoline, or rifaximin is suggested.[2] Refractory IBS is characterized by continuing symptoms, reduced QOL, and ongoing medical appointments despite treatment. In patients with refractory IBS, pain is frequently a major concern. Often, patients have comorbid psychiatric conditions. Therefore, management of symptoms requires a multidisciplinary approach with medication and nonpharmacologic management, including psychological therapy.[2]

The management of IBS is challenging because its pathogenesis is not completely understood. There is evidence that GI motility and secretion, visceral hypersensitivity, abnormalities of the enteroendocrine and immune systems, genetics, infections, changes in the intestinal microflora, and inflammation may all play a role in its pathogenesis, suggesting there are areas for further research.[21]

Nonpharmacologic Management

Nonpharmacologic interventions that reduce symptoms of IBS include patient education; reassurance by clinicians; regular exercise, including walking and yoga; and stress management through meditation, counseling, and sufficient sleep.[7] Although dietary modifications have not been proved to improve symptoms of IBS, dietary changes are reasonable for individuals for whom specific foods appear to initiate symptoms.[7]

For example, consumption of FODMAPs should be limited to those individuals in whom they cause bloating and gas. Other foods to avoid include excess fats, hard-to-digest carbohydrates, excess caffeine, and carbonated beverages. Adequate water and fiber intake are recommended for patients with IBS-C (**Table 1**[2]).[7]

Overview of Pharmacologic Interventions for IBS-D

Agents used for the pharmacologic management of IBS vary in their efficacy, the quality of evidence that supports their use, the length of time recommended for treatment, and their adverse event profiles. Some of these agents are not indicated (FDA approved) for IBS and are used off-label. In addition, the use of some approved agents is restricted; for example, alosetron is indicated only for women with severe IBS-D.[22]

The most current FDA Guidance for Industry on clinical evaluation of drugs for the treatment of IBS includes capturing patient-reported outcomes (PROs).[23] The FDA recommends development of

a multi-item PRO assessment instrument to capture the clinically important signs and symptoms of the IBS target population (eg, IBS-D or IBS-C), which should be studied in separate clinical trials owing to their significantly different signs and symptoms.[23] Trials should be randomized and placebo controlled and include a period of training patients on the method of PRO data collection, followed by a treatment period of at least 8 weeks for agents that will be administered on a chronic basis.[23] Recommended primary end points for IBS-D trials include abdominal pain intensity and stool consistency as both clinical trial entry criteria and in the definition of "responder" for clinical trial results.[23]

As the American Gastroenterological Association (AGA) pointed out in 2014, studies of the use of pharmacologic agents in IBS have generally used placebos as comparators (controls), and as a result, there is a lack of comparative effectiveness trials in patients with IBS.[20] It is a challenge to evaluate the comparative effectiveness of different pharmacological agents due to the variation among study end points across clinical trials. For example, prior to the FDA-defined criteria for responder to pharmacological IBS-D therapy in 2012, adequate global relief was considered a critical efficacy outcome in clinical trials. Trials may inconsistently report outcomes which make it difficult to assess across agents for effectiveness (ie, quality of life improvements, abdominal pain, frequency of bowel movements, stool consistency).[20] Although some treatments have limited benefit in the short term, there are no interventions that alter the long-term natural history of IBS, nor is there agreement on a gold standard for treatment of this condition. The high rate of response to placebo in IBS trials complicates clinical trial end points.[21,24]

It is not possible to directly compare the results of the clinical trials for current IBS therapeutics because these trials were conducted at different times, enrolled diverse patient populations, used varying diagnostic criteria for IBS, and defined responses and end points differently.[24] Nevertheless, in evaluating pharmacologic treatments for IBS and selecting agents for use for individual patients, adverse events and the number needed to harm (NNH) should be taken into account.[25] The NNH is a measure of the relative risk of adverse events (AEs) and evaluates the number of patients needed to be treated (NNT) to observe an AE or harm. Although AEs vary in severity and clinical significance, discontinuation of treatment can be considered highly suggestive of significant AEs.[25]

The efficacy and safety of pharmacologic agents for IBS, including data for harm events, where available, are discussed in detail in the next sections. Both the AGA and the American College of Gastroenterology (ACG) discuss the use of these agents in their guidelines for the management of IBS. It should be noted that the most recent guidelines from both the AGA and ACG were published in 2014[20,26] and therefore predate the approval of eluxadoline and rifaximin for IBS-D.[27]

Clinical Efficacy and Safety of Off-Label Pharmacologic Agents for IBS-D

A number of pharmacologic agents have been used to treat IBS-D despite lack of approval by the FDA for this indication; therefore, use of the agents discussed in this section is considered off-label. These agents include antidepressants, smooth muscle antispasmodics, and a synthetic, opioid receptor agonist antidiarrheal agent.

Antidepressants

Two classes of antidepressants, tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs), are used in IBS. Although they may take weeks to work and their mechanism(s) of action are not entirely clear, the doses used to treat IBS are lower than those used to treat depression.[7]

TCAs used in IBS include desipramine and amitriptyline.[7] In a meta-analysis of 11 heterogeneous randomized controlled trials (RCTs) in IBS (N = 744), 43.3% of patients receiving TCAs had no symptom improvement compared with 63.7% of patients receiving placebo. The NNT with TCAs was 4 (95% CI, 3-6).[28]

In a small study of 54 patients with IBS-D, of whom 50 completed 2 months of treatment, patients who received amitriptyline had significantly greater improvement in symptoms of loose stool and feelings of incomplete defecation and greater complete response of loss of all symptoms compared with those receiving placebo (68% vs 28%, respectively; $P = .01$).[29]

The adverse effects (AEs) of TCAs include fatigue and drowsiness, though these AEs may be desirable as they improve sleep when taken at night.[7] It has been observed in one study that patients receiving antidepressants were about twice as likely to experience AEs as those receiving placebo (31.3% vs 16.5%, respectively) with the most common being drowsiness and dry mouth.[28] The increased incidence of AEs was not seen with low-dose amitriptyline use compared to placebo.[29]

It should be noted that TCAs like amitriptyline have boxed warnings about suicidality.[30] The ACG notes that patients may find AEs associated with antidepressants to be intolerable.[26]

SSRIs used in IBS include paroxetine, citalopram, escitalopram, fluoxetine, fluvoxamine, sertraline, and others. In a meta-analysis of 7 RCTs (N = 356), 45.5% of patients receiving SSRIs had no improvement in their symptoms after therapy compared with 67.2% of patients receiving placebo. The NNT with SSRIs was 4 (95% CI, 2.5-20).[28] Overall, the AGA finds the quality of evidence from RCTs to be low for the use of TCAs or SSRIs in the management of IBS.[20]

Smooth Muscle Antispasmodics

Smooth muscle antispasmodics include dicyclomine and hyoscyamine.[7] These agents have been used empirically for IBS and may provide short-term symptomatic relief.[26] Antispasmodics are used as needed to alleviate abdominal spasms and cramps and to

TABLE 2. Phase 3 Safety and Efficacy of Pharmacologic Interventions Indicated for IBS-D[22, 32-40]

Agent	MOA	Phase 3 Trials	
		Treatment	Number of Patients
Alosetron	5-HT_3 receptor antagonist; inhibits colon motility and secretion	Alosetron 1 mg twice daily vs placebo for 48 weeks	N = 714 • Alosetron: n = 351 • Placebo: n = 363
Eluxadoline	Mu-opioid receptor agonist, delta-opioid receptor antagonist, kappa opioid receptor agonist	**IBS-3001** Eluxadoline 75 mg or 100 mg twice daily vs placebo for 26 weeks	N = 1282 • Eluxadoline 75 mg: n = 429 • Eluxadoline 100 mg: n = 426 • Placebo: n = 427
		IBS-3002 Eluxadoline 75 mg or 100 mg twice daily vs placebo for 52 weeks	N = 1146 • Eluxadoline 75 mg: n = 381 • Eluxadoline 100 mg: n = 383 • Placebo: n = 382
Rifaximin	Nonaminoglycoside, semisynthetic, nonsystemic antibiotic derived from rifamycin SV	**TARGET 1** 550 mg vs placebo 3 times daily for 2 weeks, (then 10 weeks of follow-up without treatment)	N = 623 • Rifaximin: n = 309 • Placebo: n = 314
		TARGET 2 550 mg vs placebo 3 times daily for 2 weeks, (then 10 weeks of follow-up without treatment)	N = 637 • Rifaximin: n = 316 • Placebo: n = 321
		Combined analysis of TARGET 1 and TARGET 2	N = 1260 • Rifaximin: n = 625 • Placebo: n = 635
		TARGET 3 550 mg vs placebo 3 times daily for 2 weeks, for patients who were responders during open-label treatment phase (rifaximin 550mg 3 times daily for 2 weeks). Followed by 550 mg vs placebo 3 times daily for 2 weeks	N = 636 • Rifaximin: n = 328 • Placebo: n = 308

AE indicates adverse effect; IBS, irritable bowel syndrome; IBS-D, irritable bowel syndrome with prominent diarrhea; MOA, mechanism of action.
[a]Based on Wholesale Acquisition Cost.

Phase 3 Trials (continued)			
Primary End Point	**Efficacy Outcomes**	**Associated Serious AEs**	**Monthly Cost[a]**
Proportion of patients with adequate relief of pain and discomfort (48-week average)	• Alosetron: 51.6% • Placebo: 40.9% (*P* = .005)	Constipation, nausea, vomiting, abdominal pain/discomfort, gastroenteritis Black box warning for serious gastrointestinal AEs, including ischemic colitis and serious complications of constipation	$360-$2826 (for 60 1-mg tablets)
Proportion of patients with composite response at weeks 12 and 26 (≥30% reduction from average baseline score of worst abdominal pain plus stool-consistency score of <5 on ≥50% of the days)	12 weeks: • 75 mg: 23.9% • 100 mg: 25.1% • Placebo: 17.1% (*P* = .01 for 75 mg) (*P* = .004 for 100 mg) 26 weeks: • 75 mg: 23.4% • 100 mg: 29.3% • Placebo: 19.0% (*P* = .11 for 75 mg) (*P* <.001 for 100 mg)	Pancreatitis, sphincter of Oddi spasm	$1145 (for 60 75-mg or 60 100-mg tablets)
	12 weeks: • 75 mg: 28.9% • 100 mg: 29.6% • Placebo: 16.2% (*P* <.001 for both doses) 26 weeks: • 75 mg: 30.4% • 100 mg: 32.7% • Placebo: 20.2% (*P* = .001 for 75 mg) (*P* <.001 for 100 mg)		
Proportion of patients with adequate relief of global IBS symptoms for ≥2 of 4 weeks during primary evaluation period (weeks 3 through 6)	• Rifaximin: 40.8% • Placebo: 31.2% (*P* = .01)	Increased hepatic enzymes, increased phosphokinase, clostridium colitis	$1358 (for 42 550-mg tablets)
	• Rifaximin: 40.6% • Placebo: 32.2% (*P* = .03)		
	• Rifaximin: 40.7% • Placebo: 31.7% (*P* <.001)		
Proportion of patients who had a response in both abdominal pain and stool consistency occurring at the same time during the first 4 weeks after the second course of treatment	• Rifaximin: 38.1% • Placebo: 31.5% (*P* = .03)		

reduce pain by decreasing smooth muscle contraction. Common AEs include dry mouth, dizziness, and blurred vision of which the latter two are known to impact some activities of daily living (eg, driving and certain work functions).[7] Both the AGA and the ACG have determined that the quality of evidence for the use of these agents is low.[20,26]

Loperamide

Loperamide is a synthetic opioid receptor agonist used as an antidiarrheal agent in patients with IBS-D and is available over the counter.[31] However, although loperamide is effective in this regard, the ACG has determined that there is no evidence to support its use for the relief of symptoms of IBS.[26] Likewise, the AGA found the quality of evidence for the use of loperamide to be very low. In addition, the 2 small, double-blind, placebo-controlled studies that evaluated the efficacy of loperamide in IBS did not define the diagnostic criteria for IBS, and the overall evidence was considered to be subject to serious risk of bias, imprecision, and suspected publication bias.[20]

Clinical Efficacy and Safety of Pharmacologic Agents Indicated for IBS-D

The pharmacologic agents that are indicated by the FDA for the treatment of IBS-D should be used on the basis of patient symptoms, severity of symptoms, medical history, mechanism of action, cost, availability, insurance coverage, and AE profile.[24] The mechanisms of action, efficacy, and safety of these agents in phase 3 clinical trials, as well as their monthly prescription costs, are summarized in **Table 2**.[22,32-40]

Alosetron

Alosetron (Lotronex) is a selective serotonin 5-HT_3 antagonist indicated only for women with severe IBS-D.[22] A 12-week double-blind, placebo-controlled, parallel-group study enrolled 462 patients with IBS, 335 of whom were female, and evaluated 3 doses of alosetron.[41] The 2-mg twice-daily dose significantly increased the proportion of pain-free days and decreased the visual analogue scale score for diarrhea compared with placebo in the overall population.[41]

In a phase 3 trial comparing the long-term efficacy and safety of alosetron treatment (n = 279) with placebo (n = 290) in a subgroup of women with IBS-D,[32] alosetron was associated with significant relief of abdominal pain and discomfort compared with placebo for 10 of the 12 months of treatment. The average rate of adequate relief was 10.7% greater in patients treated with alosetron versus placebo; this was associated with an NNT of 9 (95% CI, 6-30).[32] AEs occurred in 85% of patients receiving alosetron versus 72% receiving placebo (P <.001); of these, 33% and 16% were deemed to be drug related, respectively.[32]

The AGA recommends alosetron for women whose IBS-D symptoms have not responded to conventional therapy and who have severe symptoms, defined as at least 1 of the following: frequent and severe abdominal pain or discomfort, frequent bowel urgency or incontinence, and/or disability or restriction of daily activities resulting from IBS. There is a high quality of evidence for adequate relief of abdominal pain and discomfort from 8 RCTs, the results of which show clinically meaningful improvement in global pain relief and abdominal pain responses.[20]

It should be noted that using alosetron requires participation in a Risk Evaluation and Mitigation Strategy (REMS) program because of the potential for serious risks of ischemic colitis and serious complications of constipation associated with the agent.[42] A pooled analysis of clinical trial safety data for approximately 12,000 patients showed that treatment with alosetron increased the incidence of ischemic colitis compared with placebo (0.15% vs 0.0%, respectively; P = .03), or 6.4 cases of ischemic colitis for every 1000 patient-years of treatment with alosetron.[43] Alosetron treatment was associated with 31 cases of serious complications of constipation; 26% of cases occurred within 7 days of treatment. Of these 31 patients, 29 were hospitalized, 10 underwent surgery, and 2 died. In 3 individuals, serious complications of constipation were associated with ischemic colitis.[43]

Eluxadoline

Eluxadoline (Viberzi) is a mu-opioid receptor agonist that received FDA approval in 2015.[33] In 2 phase 3, parallel-group, randomized, placebo-controlled, multicenter trials (IBS-3001 and IBS-3002), eluxadoline 75 mg and 100 mg were compared with placebo in 2428 adults with IBS-D.[44] The primary efficacy end point was the proportion of patients with a composite response of simultaneous improvement in abdominal pain and reduction in diarrhea.[44]

The composite responder rate remained significantly higher for both doses of eluxadoline than for placebo over weeks 1 through 12 and 1 through 26. Previous use of loperamide was reported by 36.0% of patients. Of these, 67.1% who were randomized to eluxadoline 75 mg and 58.8% randomized to eluxadoline 100 mg reported inadequate IBS-D symptom control with loperamide.[44] For these patients, the composite responder rate remained significantly higher for both doses of eluxadoline (75 mg: 26.3% [P = .001]]; 100 mg: 27% [P <.001]) than for placebo (12.7%) over weeks 1 through 12.[40] Loperamide rescue was allowed during the trial and overall, eluxadoline was associated with higher response rates than placebo.[44]

Secondary end points in these 2 phase 3 eluxadoline trials included pain relief, improvement in stool consistency, improvement in global symptom scores, and adequate relief of IBS symptoms.[34] There were no significant improvements for the worst abdominal pain or in the proportion of patients reporting improvement of at least 30% in scoring for the worst abdominal pain.[34] From weeks 1 through 12 of the IBS-3001 trial, 35.1% of patients treated with 75-mg eluxadoline and 34.7% of patients treated with the 100-mg dose experienced an

IBS-D global symptom response compared with 28.8% of patients receiving placebo. Adequate relief of IBS symptoms was reported in significantly more patients treated with 75-mg eluxadoline versus placebo (52.9% vs 43.8%, respectively; $P = .008$) and 100-mg eluxadoline versus placebo (54.2% vs 43.8%; $P = .002$).[34]

Common AEs included constipation, nausea, and abdominal pain and were more frequent in the eluxadoline groups than in the placebo group, although still generally low.[44] Discontinuation of eluxadoline or placebo due to AEs was rare. Discontinuation due to constipation in the eluxadoline 75-mg group, eluxadoline 100-mg group, and the placebo group occurred in 1.1%, 1.7%, and 0.2% of patients, respectively; the rates of discontinuation due to nausea were 0.6%, 0%, and 0.5%, respectively. There were no deaths. One patient experienced ischemic colitis at the 100-mg dose of eluxadoline. Serious AEs occurred in 4.2% of patients in the 75-mg group, 4.8% of patients in the 100-mg group, and 3.0% of patients in the placebo group.[34]

In 2017, the FDA released a Drug Safety Communication regarding an increased risk of serious pancreatitis that could result in hospitalization or death associated with the use of eluxadoline in patients without a gallbladder. From May 2015, when eluxadoline was initially approved, to February 2017, 120 cases of pancreatitis were reported, some occurring after the initial dose. Of these, 76 resulted in hospitalization; 2 of the hospitalized patients died.[45]

Rifaximin

Rifaximin (Xifaxan) is an oral antibiotic indicated for the treatment of IBS-D in adults.[35] The safety and efficacy of rifaximin were demonstrated in patients with IBS without constipation in 2 phase 3 double-blind placebo-controlled trials, TARGET 1 and TARGET 2. A total of 1260 patients were enrolled and assigned to TARGET 1 (n = 623) or TARGET 2 (n = 637). Within each trial, patients were randomly assigned 1:1 to 550 mg of rifaximin (n = 309 in TARGET 1; n = 316 in TARGET 2) or placebo (n = 314 in TARGET 1; n = 321 in TARGET 2) 3 times daily for 2 weeks, and then followed for an additional 10-week observation period.[36]

The primary end point was a PRO of global IBS symptom relief, where adequate relief was clinically relevant for at least 2 weeks during a month of treatment-free follow-up.[36] A separate exploratory composite end point requested by the FDA was added to determine the proportion of patients who experienced relief, defined as a decrease of at least 30% from baseline in weekly IBS-related abdominal pain or discomfort and a weekly stool consistency score of less than 4 (with 4 indicating loose stools and lower scores indicating more formed stools) for at least 2 weeks during a month of treatment-free follow-up.[36]

For at least 2 of the 4 weeks following the 14 days of treatment, significantly more patients who received rifaximin experienced relief of global IBS symptoms compared with those who received placebo (40.7% vs 31.7%, respectively; $P < .001$; TARGET 1 and 2 studies combined).[36] For the composite end point of IBS-related abdominal pain and stool consistency, the pooled analysis of patients in both trials showed a significant benefit with rifaximin use compared with placebo ($P < .001$); a greater proportion of patients treated with rifaximin had improved stool consistency and daily abdominal pain, assessed as individual components.[36] Patients treated with rifaximin sustained adequate relief, or durable IBS-D symptom relief, for weeks 3 through 6 of the study, as well as for the entire 3-month study period, compared with placebo ($P < .001$ in the pooled analysis).[36]

In the 12-week TARGET 1 and 2 trials, serious AEs were reported in 1.6% of patients treated with rifaximin compared with 2.4% of patients who received placebo.[36] The most common serious AEs, occurring in at least 2 patients from each treatment group, were chest pain, breast cancer, and cholecystitis; these AEs were not treatment related. Neither *Clostridium difficile*–associated diarrhea nor ischemic colitis were reported, and there were no deaths.[36]

TARGET 3 Trial

In the TARGET 3 trial, the efficacy and safety of repeat treatment with rifaximin was investigated in patients with IBS-D. A total of 2579 patients was enrolled in the open-label treatment phase, in which patients received an initial 2-week course of 550 mg rifaximin 3 times daily and were followed for an additional 4-week, treatment-free period. Patients were assessed for response to treatment at the end of the 4-week follow-up period.[40] The primary efficacy end point was the percentage of patients who had a response in both abdominal pain and stool consistency occurring at the same time during the first 4 weeks after the second course of treatment (ie, repeat treatment with either rifaximin or placebo after responding to the initial 2-week open-label course of rifaximin).[40]Rifaximin responders in the open-label phase, determined based on an evaluation of the composite end point 4 weeks after active treatment discontinuation, were followed for an additional observation period of 18 treatment-free weeks. Patients who did not respond to rifaximin in the open-label phase were withdrawn from the study.[40]Response was defined as at least 30% improvement from baseline in mean weekly abdominal pain score by a PRO scale from 0 to 10 (no abdominal pain to worst pain imaginable) and at least 50% reduction in the number of days per week the patient had BSFS type 6 or 7 stool for at least 2 of the first 4 weeks after treatment.[40]

A total of 1074 patients (44.1%) responded to rifaximin in the open-label phase.[40] Of these patients, 35.6% (n = 382) had a sustained response to rifaximin and did not experience recurrence of symptoms in the treatment-free follow-up period. They were not included in the subsequent double-blind repeat treatment phase.[40]

During the observation phase, 64.4% (n = 692) of patients experienced a relapse of symptoms, with a median time to symptom recurrence of 10 weeks (range, 6 to 24 weeks); 636 of these patients

TABLE 3. NNT and NNH Across IBS-D Trials[32,46]

Treatment	Study duration	NNT	NNH[a]	NNT:NNH ratio
Alosetron	48 weeks	9	8	1.125
Eluxadoline	26 weeks	8.7	23.3	0.373
Rifaximin	10 weeks	10.6	8971	0.001

IBS-D indicates irritable bowel syndrome with prominent diarrhea; NNH, number needed to harm; NNT, number of patients needed to be treated.
[a]NNH for alosetron is the reciprocal of the treatment difference between alosetron and placebo for any adverse effects; NNH for eluxadoline includes patients who experienced an adverse event(s) that prompted discontinuation.

were randomly assigned to the double-blind, placebo-controlled, retreatment phase of the TARGET 3 trial.[35,40]

Baseline IBS symptom scores were similar in the groups of patients randomized to the rifaximin and placebo treatment arms at the time of recurrence of IBS symptoms and at randomization to the double-blind phase. Notably, baseline symptom scores were significantly lower (P <.001) at the time of randomization to the double-blind retreatment phase compared with symptom scores reported at entry to the initial open-label treatment phase. For example, at randomization to the double-blind retreatment phase, patients reported less severe abdominal pain (mean 20% improvement) compared with abdominal pain severity reported before entry into the open-label rifaximin treatment phase.[35,40] At baseline, the number of days per week with a BSFS type 6 or 7 stool was similar across all groups.[40]

Patients in the double-blind phase received a 14-day cycle of rifaximin (n = 328) or placebo (n = 308) 3 times daily, followed by a treatment-free evaluation period of 4 weeks and an additional 6-week observation period. Then, a second retreatment phase was conducted.[40] More patients experienced a response after rifaximin treatment compared with those treated with placebo (38.1% vs 31.5%, respectively; P = .03). Rifaximin was also more effective than placebo in alleviating abdominal pain (50.6% vs 42.2%; P = .018). Stool consistency response was similar in both groups (51.8% vs 50.0%; P = .42).[40] For the secondary end points, the percentage of patients without recurrence was higher with rifaximin than placebo (13.2% vs 7.1%, respectively; P = .007), and more patients experienced a durable response to rifaximin compared with placebo (17.1% vs 11.7%; P = .04).[40]

In the open-label treatment phase with rifaximin (N = 2579), 3.3% of patients (n = 85) experienced treatment-related AEs. The most common AEs included nausea (2%), headache (1.6%), upper respiratory infection (1.6%), urinary tract infection (1.4%), and nasopharyngitis (1.4%). Of the patients who experienced recurrent IBS-D symptoms (those in the double-blind treatment population), treatment-related AEs were reported in 1.8% of patients in the rifaximin group and in 2.6% of the placebo group. The most common AEs reported at a higher incidence with rifaximin compared with placebo in the double-blind phase included nausea (3.7% vs 2.3%, respectively), upper respiratory infection (3.7% vs 2.6%), nasopharyngitis (3.0% vs 2.9%), bronchitis (2.7% vs 1.6%), diarrhea (2.1% vs 1.0%), influenza (2.1% vs 0.6%), increased alanine aminotransferase (2.1% vs 1.3%), increased blood creatinine (2.7% vs 1.0%), and increased aspartate aminotransferase (2.1% vs 1.3%).[40]

Comparison of NNT and NNH for Agents Indicated for IBS-D

The NNT ranged from 9 to 11 across trials of approved agents. However, the NNH was very different across trials, ranging from 8 with alosetron and 23.3 with eluxadoline to 8971 with rifaximin.[32,46] The ratio of greater potential benefit to risk of AEs favors rifaximin over the other 2 approved agents (**Table 3**[32,46]).

Costs of IBS-D and Pharmacoeconomic Analysis of Treatments

IBS-D poses a substantial economic burden on the US healthcare system.[47] Costs associated with IBS-D are driven by several factors, including a significantly higher monthly (30-day) prescription fill rate, mean annual number of physician office visits, mean annual number of emergency department (ED) visits, and mean annual number of all-cause hospitalizations.[47] Annual indirect costs for patients with IBS-D versus controls without a diagnosis are higher for presenteeism ($5402 vs $3518, respectively; P <.001), absenteeism ($1642 vs $977; P <.05), and overall work productivity loss ($7008 vs $4522; P <.001).[17]

In a retrospective claims analysis, 39,306 commercially insured patients with IBS-D and controls without IBS-D were matched 1:1 by demographic characteristics. In this study, patients with IBS-D experienced more general and GI-related comorbidities than the unaffected matched population and used significantly more healthcare resources than matched controls.[47] After adjusting for demographic characteristics and comorbidities, compared with the unaffected controls, patients with IBS-D had significantly higher total all-cause healthcare costs ($9436 vs $7169; P <.001).[47] IBS-D related healthcare costs also were $2268 higher than expenses for those without IBS-D; 78% ($1768) of healthcare costs attributable to IBS-D were from medical costs, with the remaining 22% ($499) from prescription costs.[47]

Diagnostic tests contribute to the costs associated with IBS-D. A survey of 9 gastroenterologists, primarily from academic centers, was used to determine costs associated with a diagnosis of IBS-D. The average cost associated with an IBS diagnostic blood panel was $500 per patient, and procedure costs ranged from $189 for a small-bowel follow-through to $2727 for a colonoscopy.[48] A cost-minimization decision tree model suggests that using diagnostic blood panel testing for anti-CdtB and anti-vinculin antibodies would result in a savings of $509 per patient because the use of this panel would eliminate the use of additional tests, such as a colonoscopy.[48]

Inadequate symptom control in patients with IBS-D also causes an economic burden. In a separate retrospective analysis of administrative medical and pharmacy claims data, investigators evaluated the association between inadequate IBS-D symptom control and healthcare costs within 1 year of initial prescription treatment for IBS-D.[49] A total of 20,624 commercially insured patients with IBS-D was identified. Patients were analyzed by evidence of uncontrolled symptoms associated with the use of available treatments for IBS-D and healthcare utilization.[49]

Measures of inadequate symptom control included switching from one IBS-D symptom-related treatment to another, adding another IBS-D symptom-related treatment to the current regimen, IBS-D-related inpatient or ED admission, diagnosis of a condition indicating treatment failure, surgery or medical procedure indicating treatment failure, or use of a more aggressive prescription while on the index treatment.[49] Patients with IBS-D within the 2 cohorts of inadequate symptom control versus adequate symptom control were matched by demographics and comorbidities for analysis of healthcare usage and financial burden.[49] Outcome measures included total all-cause healthcare resource utilization and all-cause healthcare costs (all medical and pharmacy claims associated with any condition) per year.[49]

The majority of patients with IBS-D (66.4%) met the criteria for inadequate symptom control, indicating a substantial need for effective treatment for these patients.[49] Patients with uncontrolled symptoms of IBS-D endured significantly greater annual all-cause healthcare costs, with a total that was $3065 higher than for patients with IBS-D with controlled disease ($14,156 vs $11,091; 95% CI, $2378-$3751; $P < .01$).[49] Medical costs were the main driver of the total annual costs in both groups of patients with IBS-D, where 78% ($2391) were from medical costs associated with increased hospitalizations, ED visits, outpatient services, and physician office visits and 22% ($674) were from prescriptions.

Healthcare resource usage was significantly higher in patients whose symptoms of IBS-D were not adequately controlled compared with those whose symptoms were controlled ($P < .01$). These measures included a significantly higher hospitalization rate (12.0% vs 6.0%, respectively); more ED visits (37.1% vs 22.6%); increased use of outpatient services, including laboratory and diagnostic testing (73.0% vs 60.7%); more physician office visits (11.0 vs 8.1); more prescription fills per year (40.0 vs 26.7); and a greater mean number of monthly (30-day) prescription fills per year (28.2 vs 19.2).[49]

Of the patients meeting the criteria for inadequate symptom control (n = 13,691), 26.7% received a diagnosis for conditions other than IBS-D, which indicated treatment failure while receiving treatment for IBS-D (eg, constipation, GI malignancy, Crohn disease, chronic gastritis, diarrhea, and small intestine bacterial overgrowth), and 31.6% underwent surgery or a medical procedure for a condition other than IBS.[49] Switching from one IBS-D treatment to another was the most common indicator of inadequate symptom control, occurring in a majority of patients (76%) who met these criteria during the study period.[49] Just over half (50.4%) of all patients with IBS-D switched from their index treatment.[49]

A cost-effectiveness comparison of the 3 FDA-approved therapies for IBS-D determined that the management cost per quality-adjusted life-year (QALY) versus placebo was $21,457 for rifaximin and $138,111 for alosetron.[50] Rifaximin was preferred by 80% of patients in a willingness-to-pay analysis from available clinical trial data and Red Book average wholesale prices.[50] The incremental cost-effectiveness ratio was lowest for rifaximin compared with alosetron or eluxadoline (rifaximin over eluxadoline by $291,123; eluxadoline over alosetron by $482,767).[50]

Conclusion

IBS is associated with substantial burden, including direct medical costs and indirect costs. Direct costs associated with IBS in the United States have been estimated to be over $1 billion, and indirect costs, such as negative effect on QOL and work productivity, are difficult to quantify.[2] The negative impact of IBS-D symptoms on QOL reported by patients indicates there is an unmet need for therapies that effectively treat and manage the symptoms of this condition.[17] Addressing gaps in treatment is an important priority.

IBS should be managed using an evidence-based approach that identifies appropriate treatments based on available data. Standardization of primary end points for IBS clinical trials would help in this area.[20] The development of disease-specific biomarkers would aid not only in diagnosis but also in the development of both pharmacologic and nonpharmacologic interventions, as will the use of standardized and validated PRO tools.[19,20] ■

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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. doi: 10.1016/j.cgh.2012.02.029.
2. Ford AC, Lacy BE, Talley NJ. Irritable bowel syndrome. *N Engl J Med*. 2017;376(26):2566-2578. doi: 10.1056/NEJMra1607547.
3. Lacy BE, Mearin F, Chang L, et al. Bowel disorders. *Gastroenterology*. 2016;150(6):1393-1407. doi: 10.1053/j.gastro.2016.02.031.
4. 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(6):892-899. doi: 10.1038/ajg.2016.574.

5. Canavan C, West J, Card T. The epidemiology of irritable bowel syndrome. *Clin Epidemiol*. 2014;6:71-80. doi: 10.2147/CLEP.S40245.
6. Spiegel BMR, 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. doi: 10.1038/ajg.2010.47.
7. Sultan S, Malhotra A. Irritable bowel syndrome. *Ann Intern Med*. 2017;166(11):ITC81-ITC96. doi: 10.7326/AITC201706060.
8. Pimentel M, Morales W, Rezaie A, et al. Development and validation of a biomarker for diarrhea-predominant irritable bowel syndrome in human subjects. *PLoS ONE*. 2015;10(5):e0126438. doi: 10.1371/journal.pone.0126438.
9. Menees SB, Powell C, Kurlander J, Goel A, Chey WD. A meta-analysis of the utility of C-reactive protein, erythrocyte sedimentation rate, fecal calprotectin, and fecal lactoferrin to exclude inflammatory bowel disease in adults with IBS. *Am J Gastroenterol*. 2015;110(3):444-454. doi: 10.1038/ajg.2015.6.
10. Slattery SA, Niaz O, Azia Q, Ford AC, Farmer AD. Systematic review with meta-analysis: the prevalence of bile acid malabsorption in the irritable bowel syndrome with diarrhoea. *Aliment Pharmacol Ther*. 2015;42(1):3-11. doi: 10.1111/apt.13227.
11. Spiller R, Garsed K. Postinfectious irritable bowel syndrome. *Gastroenterology*. 2009;136(6):1979-1988. doi: 10.1053/j.gastro.2009.02.074.
12. Gralnek IM, Hays RD, Kilbourne A, Naliboff B, Mayer EA. The impact of irritable bowel syndrome on health-related quality of life. *Gastroenterology*. 2000;119(3):654-660. doi: 10.1053/gast.2000.16484.
13. Andrae DA, Covington PS, Patrick DL. Item-level assessment of the Irritable Bowel Syndrome Quality of Life Questionnaire in patients with diarrheal irritable bowel syndrome. *Clin Ther*. 2014;36(5):663-679. doi: 10.1016/j.clinthera.2014.04.009.
14. 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. doi: 10.3748/wjg.v21.i26.8103.
15. Canavan C, West J, Card T. Change in quality of life for patients with irritable bowel syndrome following referral to a gastroenterologist: a cohort study. *PLoS One*. 2015;10(10):e0139389. doi: 10.1371/journal.pone.0139389.
16. Canavan C, West J, Card T. Review article: the economic impact of the irritable bowel syndrome. *Aliment Pharmacol Ther*. 2014;40(9):1023-1034. doi: 10.1111/apt.12938.
17. Buono JL, Carson RT, Flores NM. Health-related quality of life, work productivity, and indirect costs among patients with irritable bowel syndrome with diarrhea. *Health Qual Life Outcomes*. 2017;15(35):1-8. doi: 10.1186/s12955-017-0611-2.
18. Wong RK, Drossman DA, Weinland SR, et al. Partner burden in irritable bowel syndrome. *Clin Gastroenterol Hepatol*. 2013;11(2):151-155. doi: 10.1016/j.cgh.2012.07.019.
19. Chey WD, Kurlander J, Eswaran S. Irritable bowel syndrome: a clinical review. *JAMA*. 2015;313(9):949-958. doi: 10.1001/jama.2015.0954.
20. Chang L, Lembo A, Sultan S. American Gastroenterological Association Institute technical review on the pharmacological management of irritable bowel syndrome. *Gastroenterology*. 2014;147(5):1149-1172. doi: 10.1053/j.gastro.2014.09.002.
21. Bellini M, Gambaccini D, Stasi C, Urbano MT, Marchi S, Usai-Satta P. Irritable bowel syndrome: a disease still searching for pathogenesis, diagnosis and therapy. *World J Gastroenterol*. 2014;20(27):8807-8820. doi:10.3748/wjg.v20.i27.8807.
22. Lotronex [prescribing information]. San Diego, CA: Prometheus Laboratories, Inc; 2014. lotronex.com/Documents/Lotronex_PI.pdf. Accessed November 1, 2017.
23. US Department of Health and Human Services. Guidance for Industry: irritable bowel syndrome—clinical evaluation of drugs for treatment. FDA Center for Drug Evaluation and Research. www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM205269.pdf. Published May 2012. Accessed November 1, 2017.
24. 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):311-22. doi: 10.1517/14656566.2016.1118052.
25. Shah E, Kim S, Chong K, Lembo A, Pimentel M. Evaluation of harm in the pharmacology of irritable bowel syndrome. *Am J Med*. 2012;125(4):381-393. doi: 10.1016/j.amjmed.2011.08.026.
26. 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. doi: 10.1038/ajg.2014.187.
27. FDA approves two therapies to treat IBS-D [news release]. Silver Spring, MD: FDA; May 27, 2015. www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm448328.htm. Accessed November 1, 2017.
28. Ford AC, Quigley EMM, 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. doi: 10.1038/ajg.2014.148.
29. 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. doi: 10.1111/j.1365-2036.2008.03633.x.
30. Amitriptyline [prescribing information]. Princeton, NJ: Sandoz; 2014. www.accessdata.fda.gov/drugsatfda_docs/label/2014/085966s095,085969s084,085968s096,085971s075,085967s076,085970s072lbl.pdf. Accessed November 1, 2017.
31. Imodium capsules [prescribing information]. New Brunswick, NJ: Johnson & Johnson Consumer Inc; 2016. www.accessdata.fda.gov/drugsatfda_docs/label/2016/017690s005lbl.pdf. Accessed November 1, 2017.
32. Chey WD, Chey WY, Heath AT, et al. Long-term safety and efficacy of alosetron in women with severe diarrhea-predominant irritable bowel syndrome. *Am J Gastroenterol*. 2004;99(11):2195-2203. doi: 10.1111/j.1572-0241.2004.30509.x.
33. Viberzi [prescribing information]. Irvine, CA: Allergan USA, Inc; 2017. allergan.com/assets/pdf/viberzi_pi. Accessed November 1, 2017.
34. Lembo AJ, Lacy BE, Zuckerman MJ, et al. Eluxadoline for irritable bowel syndrome with diarrhea. N Engl *J Med*. 2016;374(3):242-253. doi: 10.1056/NEJMoa1505180.
35. Xifaxan [prescribing information]. Raleigh, NC: Salix Pharmaceuticals, Inc; 2015. shared.salix.com/shared/pi/xifaxan550-pi.pdf. Accessed November 1, 2017.
36. Pimentel M, Lembo A, Chey WD, et al; TARGET Study Group. Rifaximin therapy for patients with irritable bowel syndrome without constipation. *N Engl J Med*. 2011;364(1):22-32. doi: 10.1056/NEJMoa1004409.
37. Alosteron HCl. RED BOOK Online. Micromedex Healthcare Series [database online]. Greenwood Village, CO: Truven Health Analytics; 2018. Accessed January 12, 2018.
38. Viberzi. RED BOOK Online. Micromedex Healthcare Series [database online]. Greenwood Village, CO: Truven Health Analytics; 2018. Accessed January 12, 2018.
39. Xifaxan. RED BOOK Online. Micromedex Healthcare Series [database online]. Greenwood Village, CO: Truven Health Analytics; 2018. Accessed January 12, 2018.
40. Lembo A, Pimentel M, Rao SS, et al. Repeat treatment with rifaximin is safe and effective in patients with diarrhea-predominant irritable bowel syndrome. *Gastroenterology*. 2016;151(6):1113-1121. doi: 10.1053/j.gastro.2016.08.003.
41. Bardhan KD, Bodemar G, Geldof H, et al. A double-blind, randomized, placebo-controlled dose-ranging study to evaluate the efficacy of alosetron in the treatment of irritable bowel syndrome. *Aliment Pharmacol Ther*. 2000;14(1):23-34.
42. NDA 21-107: Risk evaluation and mitigation strategy (REMS). FDA website. www.accessdata.fda.gov/drugsatfda_docs/rems/Lotronex_2016-04-29_REMS_full.pdf. Updated April 2016. Accessed November 1, 2017.
43. Chang L, Chey W, 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. doi: 10.1111/j.1572-0241.2006.00459.x.
44. Lacy BE, Chey WD, Cash BD, Lembo AJ, Dove LS, Covington PS. Eluxadoline efficacy in IBS-D patients who report prior loperamide use. *Am J Gastroenterol*. 2017;112(6):924-932. doi: 10.1038/ajg.2017.72.
45. Drug safety communications: FDA warns about an increased risk of serious pancreatitis with irritable bowel drug Viberzi (eluxadoline) in patients without a gallbladder. www.fda.gov/downloads/Drugs/DrugSafety/UCM546542.pdf. Published March 15, 2017. Accessed November 1, 2017.
46. Lucak S, Chang L, Halpert A, Harris LA. Current and emergent pharmacologic treatments for irritable bowel syndrome with diarrhea: evidence-based treatment in practice. *Ther Adv Gastroenterol*. 2017;10(2):253-275. doi: 10.1177/1756283X16663396.
47. Buono JL, Mathur K, Averitt AJ, Andrae DA. Economic burden of irritable bowel syndrome with diarrhea: retrospective analysis of a U.S. commercially insured population. *J Manag Care Spec Pharm*. 2017;23(4):453-460. doi: 10.18553/jmcp.2016.16138.
48. Pimentel M, Purdy C, Magar R, Rezaie A. A predictive model to estimate cost savings of a novel diagnostic blood panel for diagnosis of diarrhea-predominant irritable bowel syndrome. *Clin Ther*. 2016;38(7):1638-1652. doi: 10.1016/j.clinthera.2016.05.003.
49. Buono JL, Mathur K, Averitt AJ, Andrae DA. Economic burden of inadequate symptom control among US commercially insured patients with irritable bowel syndrome with diarrhea. *J Med Econ*. 2017;20(4):353-362. doi: 10.1080/13696998.2016.1269016.
50. Li YH, Gupta P, Sawant R, Sansgiry SS. A cost-effectiveness comparison of alosetron, eluxadoline, and rifaximin in the treatment of irritable bowel syndrome with diarrhea. *Pharm Pharmacol Int J*. 2016;4(6):1-9. doi: 10.15406/ppij.2016.04.00095.