# An Individualized, Case-Based Approach to the Management of Irritable Bowel Syndrome

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**Disclosure Note:** This CME activity includes discussion about medications not approved by the US Food and Drug Administration and uses of medications outside of their approved labeling.

## CONTINUING MEDICAL EDUCATION

### LEARNING OBJECTIVES

- Describe the multiple symptoms of irritable bowel syndrome (IBS) and their impact on quality of life
- Use a staged strategy for the diagnostic evaluation of IBS based on history and physical examination, including Rome IV criteria
- Individualize treatment for IBS based on an evolving understanding of pathophysiologic mechanisms using evidence-based therapies to address patient concerns and improve quality of life

### TARGET AUDIENCE

Family physicians and clinicians who wish to gain increased knowledge and greater competency regarding primary care management of irritable bowel syndrome.

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## BURDEN OF DISEASE

Irritable bowel syndrome (IBS) is a common gastrointestinal (GI) disorder that affects 10% to 15% of the US population.[1] IBS is more prevalent in women and in persons younger than 50 years.[2] IBS is characterized by recurrent abdominal pain and altered bowel habits; bloating and distention frequently coexist. Based on the predominant bowel habit pattern, IBS is classified as constipation-predominant (IBS-C), diarrhea-predominant (IBS-D), or a mixed pattern of constipation and diarrhea (IBS-M).[3]

Patients with IBS-D have significantly lower self-esteem than healthy controls[4] and patients with IBS-C.[5] Regardless of which type of IBS a patient may have, IBS sufferers report significantly greater symptom severity than patients with

inflammatory bowel disease (IBD).[6] Approximately one-third of people with IBS-D experience mild symptoms, one-half have moderate symptoms, and 1 in 8 have severe symptoms.[7] The IBS in America survey showed that three-quarters of persons with IBS symptoms tried an average of 3.6 nonprescription products before seeking medical care.[8,9] Abdominal pain was the most common reason people sought medical care.

### CASE STUDY 1

SC is a 25-year-old woman with symptoms of constipation that began in high school, persisted through college, and worsened over the last 3 years. She reports skipping 1 to 2 days without having a bowel movement; she has significant straining at stool. Her stool is often hard and difficult to evacuate. She describes pressure and pain in her lower abdomen that is present more days than not. The abdominal pain generally improves after having a bowel movement. She frequently feels bloated and jokes that her boyfriend says that she sometimes looks "pregnant" because of the gas.

Adding more fiber to her normal fiber diet (25 g/d) made her more bloated, while stool softeners provided no benefit. SC has taken large amounts of magnesium citrate, which only caused urgent diarrhea and did not help with the abdominal pain or bloating. A trial of polyethylene glycol helped the constipation, but did not improve the abdominal pain or bloating.

She reports that her weight has been stable over the last few years (body mass index [BMI] 22). Her recent gynecologic exam, including a pregnancy test and complete blood count (CBC), was normal. Her only medication is an oral contraceptive. SC has not had any abdominal surgeries and she is otherwise healthy. No family member has IBD, celiac disease, or any type of GI malignancy. Her physical exam in the office is normal other than mild discomfort in the left lower quadrant. A rectal examination, with a chaperone present, is normal.

SC asks what her diagnosis is, whether she needs a colonoscopy, and whether other treatment options are available.

## "What do you think I have? Do I need a colonoscopy?"

The diagnosis of IBS can be made by taking a careful history (medical, surgical, dietary, psychological) and asking about potential warning signs or "red flags." These signs include unexplained anemia, evidence of GI bleeding, unintentional weight loss, age >45 years without prior colon cancer screening, and family history of colorectal cancer or IBD. In addition to the history, the diagnosis is also based on a careful physical examination, ideally based on the Rome IV criteria (https://theromefoundation.org/rome-iv/whats-new-for-rome-iv/).[3] In addition to facilitating making a positive diagnosis instead of a diagnosis of exclusion, the Rome IV criteria are also useful to categorize IBS as IBS-C, IBS-D, or IBS-M.[3]

The Rome IV criteria are clinically useful for the accurate diagnosis of IBS. The criteria state that patients should have abdominal pain ≥1 day per week on average associated with ≥2 of the following symptoms: pain related to defecation, pain associated with a change in stool frequency, or pain associated with a change in stool form.[3] Symptoms should be active within the prior 3 months and should have developed at least 6 months earlier. Unlike previous Rome criteria, Rome IV criteria now suggest limited testing. This testing includes (1) a CBC to ensure the absence of anemia; (2) C-reactive protein (CRP) and/or fecal calprotectin to lower the suspicion for IBD and to prevent indiscriminate use of colonoscopy; and (3) serologic testing to rule out celiac disease.[3,10] In patients without red flag symptoms, further testing does not increase the sensitivity of the diagnosis.[11,12] Patients who may benefit from colonoscopy have warning signs or persistent symptoms, despite appropriate therapy, especially women age >60 years with persistent diarrhea, in whom microscopic colitis is a concern.

## "What is the treatment for IBS-C?"

In 2018, the American College of Gastroenterology (ACG) published updated recommendations for the treatment of IBS based on a systematic review.[13] Nonpharmacologic therapy such as fiber, nonprescription laxatives, and stool softeners generally comprise initial therapy, but treatment satisfaction is low.[8,9] Three prosecretory medications are approved in the United States for IBS-C: linaclotide and plecanatide, both of which are guanylate cyclase C agonists, and lubiprostone, a chloride channel activator. All 3 are strongly recommended by the ACG for overall symptom improvement for IBS-C based on prospective, randomized controlled trials (RCTs). The use of lubiprostone is limited to women age ≥18 years. Patients treated with a prosecretory medication should be educated about the possible occurrence of severe diarrhea requiring treatment discontinuation and rehydration.

The efficacy and safety of linaclotide are supported by 4 RCTs involving 2867 patients with IBS-C.[13] Patients treated with linaclotide were less likely to remain symptomatic compared with placebo (relative risk [RR] 0.81; 95% confidence interval [CI], 0.77-0.85). Reduction in abdominal pain was significantly greater with linaclotide.

The use of lubiprostone and plecanatide is supported by 3 RCTs for each medication involving 1366 and 2612 patients with IBS-C, respectively.[13] Patients treated with lubiprostone (RR 0.91; 95% CI, 0.87-0.95) or plecanatide (RR 0.88; 95% CI, 0.84-0.92) were less likely to remain symptomatic compared with placebo.

### CASE STUDY 1 (CONTINUED)

SC was told that, based on her history and examination, she had IBS-C. A colonoscopy was not recommended given her age and the absence of warning signs. She was started on once-daily linaclotide 290 µg. During a follow-up telephone call 2 weeks later, she reported that she was having a bowel movement each day and that her bloating and discomfort were better.

### CASE STUDY 2

HP is a 51-year-old man with an 8-year history of loose, watery, bowel movements and lower abdominal pain. Symptoms occurred after he took antibiotics for a dental procedure and developed *Clostridium difficile* colitis. He has been tested multiple times for *C. difficile* and all studies have been negative. Laboratory studies (CBC, basic metabolic panel, CRP) have been normal on multiple occasions and a recent fecal calprotectin was also normal. A screening colonoscopy, including random biopsies throughout the colon, at age 50 years was normal.

On an average day, he has 5 to 6 loose, urgent bowel movements. His lower abdominal pain improves temporarily after having a bowel movement but then returns. He describes intermittent bloating and a feeling of "gassiness." He has eliminated dairy and caffeine from his diet without benefit. Loperamide helps the diarrhea to some degree, but does not help the abdominal pain or bloating. Despite these symptoms, he has gained weight over the past 5 years and is now overweight, with a BMI of 27.

The physical examination is normal other than mild tenderness in the left lower quadrant. He is worried because a cousin had similar symptoms and was diagnosed with Crohn's disease. No first-degree family member has had colorectal cancer or IBD, although his aunt has celiac disease.

HP is frustrated and has several questions.

### "Why are my test results normal?"

This patient has had diarrhea and other symptoms for many years, but does not have any warning signs on history or physical examination (he is not anemic, has no weight loss, no history of colorectal cancer or IBD in a first-degree family member, and no serious findings on physical examination). In addition, laboratory tests and stool studies have been normal. These findings all increase the likelihood that his symptoms represent a functional GI disorder, such as IBS, rather than an organic disorder. Further evidence supporting the diagnosis of IBS are a normal CBC and CRP.

In patients with chronic diarrhea, it is also recommended that fecal calprotectin be measured to help distinguish IBS from IBD.[14] A fecal calprotectin level ≤40 µg/g combined with a normal CRP essentially excludes IBD in patients with IBS symptoms. In this patient, both a fecal calprotectin and a CRP were normal. Finally, serologic testing for celiac disease should be performed in patients with persistent diarrhea symptoms.[15] This was performed at the time of the office visit (with assurance that the patient had been ingesting some wheat-containing products within the past 2 weeks) and the results were normal, effectively excluding the diagnosis of celiac disease.

### "Why did my symptoms develop?"

The etiology and pathophysiology of IBS are complex and incompletely understood. In addition to genetics, insults to the GI tract (eg, infections, inflammation, surgery, ischemia, medications, stress) may alter the gut microbiome, disrupt the immune system, and change both GI motility and sensation.[15,16] Identification of these factors and their interaction with the brain suggest that IBS is a disorder of gut-brain interactions.[17,18]

In HP's case, the prior GI infection (*C difficile* colitis) likely led to the development of his IBS symptoms. In fact, considerable evidence indicates that a prior acute infectious gastroenteritis is the strongest risk factor for IBS, occurring in 4% to 36% of patients.[19-21] Microbial factors may exert effects on the immune system and gut barrier function, as well as the gut-brain axis.[18,22] The prevailing theory is that IBS-D is associated in some patients with bacterial overgrowth in the small intestine that impairs gut motility, whereas IBS-C is associated in some patients with increased levels of archaea that slow intestinal contractility.[22]

### "What is the role of diet in treating my symptoms?"

Many patients with IBS associate symptoms of abdominal pain, bloating, or diarrhea with eating a meal. Thus, dietary interventions appear to be a reasonable treatment approach. The addition of a soluble fiber product to the diet that has a low rate of fermentation (eg, psyllium) may improve IBS symptoms in some patients.[13] However, fiber products, especially insoluble fiber, may worsen bloating and abdominal pain. No large prospective studies have assessed the utility of soluble fiber in patients with IBS-D.[13]

The 2 diets most commonly used for the treatment of IBS are a low/no gluten diet and a low FODMAP (fermentable oligo-, di-, monosaccharide, and polyol) diet.[13,23] Routine use of a gluten-free diet is not recommended due to the low-quality evidence supporting its use.[23] Patients who note improvement on a low/no gluten diet likely improve not because they are allergic to wheat or have celiac disease, but rather because gluten contains a large amount of fructan, a short-chain carbohydrate that can cause gas, bloating, distension, and diarrhea.[24]

An analysis of 7 RCTs evaluating the efficacy of a low

FODMAP diet to treat IBS symptoms showed improvement in overall IBS symptoms compared with control diets.[23] The ACG recommends this diet as a reasonable approach, recognizing that the quality of evidence is very low.[13] It is important to remember that the elimination phase of the low FODMAP diet should be carried out for only 4 to 6 weeks, to minimize the likelihood of micronutrient deficiencies. Foods should then be reintroduced slowly.

### "What about using a probiotic to improve my symptoms?"

Because alterations in the gut microbiome can lead to symptoms of IBS, modulating the gut microbiome with a probiotic appears to make sense. Probiotics, defined as ". . . live microorganisms that, when administered in adequate amounts, confer a health benefit on the host,"[25] come in a wide array of formulations and doses. A recent meta-analysis of 53 RCTs showed that probiotics were more likely to improve symptoms of IBS compared with placebo, although the results were not overwhelming.[26] Probiotics containing a mixture of different organisms, especially those with *Lactobacillus* and *Bifidobacteria*, appear to be better than probiotics that contain only a single organism.[13,26] Based on low-quality evidence, the ACG gave probiotics, as a class, a weak recommendation.[13]

### "Will an antibiotic improve my IBS-D symptoms?"

Treating patients with IBS-D with a course of antibiotics has been shown to be effective.[27] The most commonly studied antibiotic for the treatment of IBS without constipation (both IBS-D and IBS-M) is rifaximin, a nonabsorbable antibiotic. Although its mechanism for improving IBS symptoms is unclear, several large, prospective RCTs have demonstrated that a dose of 550 mg 3 times daily for 14 days is both safe and effective (number needed to treat [NNT] = 9).[13,26,27] In contrast to other medications or diets, which need to be used chronically, a 2-week course of rifaximin may improve symptoms for up to 12 weeks.

Recognizing that IBS is a chronic condition for most patients, authors of a recent study demonstrated that repeated dosing with rifaximin was both safe and effective.[28] Because a validated treatment algorithm for the treatment of IBS-D does not exist, a precise answer of when to use rifaximin for the treatment of IBS-D symptoms cannot be provided. However, if a patient has not had symptom improvement after trying dietary therapy and over-the-counter agents, then rifaximin is a reasonable choice.

### "Are other treatment options available?"

Loperamide is often used for IBS-D, but there is little evidence to support its use and it does not improve either the cardinal symptom of IBS—abdominal pain—or bloating. Consequently, the ACG recommends against the use of loperamide to treat overall IBS symptoms.[13]

Eluxadoline acts as an agonist on the mu- and kappa-opioid receptors, while it is an antagonist on the delta-opioid receptor.[29] Three large RCTs showed that eluxadoline, at either the 75- or 100-mg dose, was more likely to improve overall IBS-D symptoms (both diarrhea and abdominal pain) than placebo (NNT=9-10).[29] Consequently, eluxadoline is recommended by the ACG to treat overall IBS-D symptoms, although the recommendation is weak because of some heterogeneity in the published studies.[13] This medication should not be used in patients who have undergone cholecystectomy or in patients who abuse alcohol, as these 2 factors are associated with the development of pancreatitis.[30] However, eluxadoline would be a reasonable treatment option for HP.

Another treatment option for IBS-D is alosetron, a serotonin antagonist. Several large, randomized placebo-controlled studies have demonstrated that alosetron can improve symptoms of abdominal pain, diarrhea, and urgency in women with symptoms of IBS-D in whom standard therapy has failed (NNT=7.5).[13,31] A more recent, real-world, dose-titration study, using the lower dose of 0.5 mg twice daily with dose escalation as needed, found an overall response rate of 45% with few adverse effects.[32] Alosetron has been associated with rare events of ischemic colitis. Alosetron is not approved for men and, thus, would not be an appropriate treatment option for this patient.

A review of the safety profile of all medications used to treat IBS-D symptoms was recently published.[33]

### CASE STUDY 3

RE is a 57-year-old woman with symptoms of alternating constipation and diarrhea. Symptoms began in her mid-40s, primarily characterized by lower abdominal pain and symptoms of constipation (skipping days without a bowel movement, hard to evacuate stool, harder stool). As there was no evidence of an organic disorder, she was diagnosed with IBS-C at the time. She was treated with polyethylene glycol and as-needed use of smooth muscle antispasmodic agents, which provided some relief of her constipation symptoms, but not much relief of her abdominal pain.

Approximately 18 months ago, RE noted that she began having 1 or 2 days per week with loose, urgent bowel movements. The other days were characterized by stool that was harder and somewhat difficult to evacuate. She increased her use of polyethylene glycol, resulting in stool that was often loose and unpredictable.

She finds that daily loperamide controls the diarrhea, but worsens the constipation and accompanying abdominal pain. Bloating is present most days and she frequently feels distended. She has not changed her diet, exercise routine, or prescription medications (levothyroxine for hypothyroidism, loratadine for mild seasonal allergies, and paroxetine for mild anxiety). She has gained approximately 1 pound per year for the past 10 years (BMI 28).

A recent gynecologic exam was normal. Because her bowel habits had changed, her gynecologist referred her for a colonoscopy, which was normal. A CBC, thyroid-stimulating hormone level, and serum tissue transglutaminase antibody with serum immunoglobulin A (IgA) also were normal. Her physical exam in the office is normal other than mild discomfort in the left lower quadrant. A rectal examination, with a chaperone present, is normal. No family member has colorectal cancer, celiac disease, or IBD.

RE is particularly bothered by bloating, and the urgent diarrhea makes it difficult to attend meetings at work and participate in social events. She is worried that the change in bowel habits represents something serious such as a hidden cancer.

### Treatment plan for this patient

The natural history of IBS and how bowel habits frequently change over time (from IBS-C to IBS-M or IBS-M to IBS-D or IBS-D to IBS-M; less commonly directly from IBS-C to IBS-D) was reviewed with RE. IBS-M occurs in approximately one-quarter of patients with IBS, while IBS-D occurs in 40% and IBS-C in 35%.[2] This patient did not have any red flags on history or exam. Recent laboratory findings, gynecologic examination, and colonoscopy were all normal. As no medication is US Food and Drug Administration approved for IBS-M, and because bloating was a predominant symptom, we decided to institute a low FODMAP diet. She did this for 4 weeks and noted a significant improvement in general IBS symptoms, although her constipation became a bit worse. Improvement of 1 symptom and worsening of another with treatment is not unusual.

RE slowly reintroduced foods per the low FODMAP protocol to identify trigger foods. We decided that she should take a little more polyethylene glycol each day for the constipation symptoms. To help with visceral pain and bowel urgency, we added a neuromodulator at a low dose, ie, amitriptyline 10 mg at bedtime. Tricyclic antidepressants have been shown to improve symptoms of abdominal pain in patients with IBS (NNT = 4.5).[13] We discussed routine scheduled bathroom time in the morning to help empty her lower colon, with the goal of minimizing symptoms of urgent diarrhea later in the day. To prevent urgent diarrhea, RE began to use one-half of a 1-mg loperamide tablet 1 hour before a business meeting or social event. After 4 weeks, she reported feeling 50% better and a bit less anxious about urgent diarrhea. This latter point underscored the importance of addressing the patient's fears and concerns as such support can dramatically improve a patient's quality of life. Having identified several foods that made her bloating much worse, she continued on the low FODMAP diet. With the goal of reducing her symptoms further, she continued on low-dose amitriptyline, but we increased the dose to 20 mg at bedtime. At her visit 4 weeks later, she reported not using any loperamide since her last visit and that she felt 80% better. Because she was generally satisfied with her symptoms, we decided to make no further changes. ●

## REFERENCES


1. International Foundation for Gastrointestinal Disorders. *Reporter's Guide to Irritable Bowel Syndrome*. 2nd edition. Published 2018. https://iffgd.org/images/library/Reporters_Guide/ReportersGuideIBS.pdf. Accessed May 12, 2020.
2. 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.e714.
3. Lacy BE, Mearin F, Chang L, et al. Bowel disorders. *Gastroenterology*. 2016;150:1393-1407.
4. Grodzinsky E, Walter S, Viktorsson L, Carlsson AK, Jones MP, Faresjo A. More negative self-esteem and inferior coping strategies among patients diagnosed with IBS compared with patients without IBS—a case-control study in primary care. *BMC Fam Pract*. 2015;16:6.
5. 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.
6. Lee AD, Spiegel BM, Hays RD, et al. Gastrointestinal symptom severity in irritable bowel syndrome, inflammatory bowel disease and the general population. *Neurogastroenterol Motil*. 2017;29(5).
7. 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(1):35.
8. The America Gastroenterological Association. *IBS in America survey summary findings*. Published December 2015. http://www.multivu.com/players/English/7634451-aga-ibs-in-america-survey/docs/survey-findings-pdf-635473172.pdf. Accessed May 14, 2020.
9. Rangan V, Ballou S, Shin A, Camilleri M, Lembo A. Use of treatments for irritable bowel syndrome and patient satisfaction based on the IBS in America survey. *Gastroenterology*. 2020;158(3):786-788.e781.
10. Ford AC, Lacy BE, Talley NJ. Irritable bowel syndrome. *N Engl J Med*. 2017;376(26):2566-2578.
11. Begtrup LM, Engsbro AL, Kjeldsen J, et al. A positive diagnostic strategy is noninferior to a strategy of exclusion for patients with irritable bowel syndrome. *Clin Gastroenterol Hepatol*. 2013;11(8):956-962.e951.
12. Engsbro AL, Begtrup LM, Kjeldsen J, et al. Patients suspected of irritable bowel syndrome—cross-sectional study exploring the sensitivity of Rome III criteria in primary care. *Am J Gastroenterol*. 2013;108(6):972-980.
13. Ford AC, Moayyedi P, Chey WD, et al. *American College of Gastroenterology Monograph on Management of Irritable Bowel Syndrome*. *Am J Gastroenterol*. 2018;113(Suppl 2):1-18.
14. 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.
15. Drossman DA. Functional gastrointestinal disorders: history, pathophysiology, clinical features and Rome IV. *Gastroenterology*. 2016;150(6):1262-1279.
16. Barbara G, Grover M, Bercik P, et al. Rome foundation working team report on post-infection irritable bowel syndrome. *Gastroenterology*. 2019;156(1):46-58.e47.
17. Drossman DA, Hasler WL. Rome IV-functional GI disorders: disorders of gut-brain interaction. *Gastroenterology*. 2016;150(6):1257-1261.
18. Chong PP, Chin VK, Looi CY, Wong WF, Madhavan P, Yong VC. The microbiome and irritable bowel syndrome—a review on the pathophysiology, current research and future therapy. *Front Microbiol*. 2019;10:1136.
19. Shah ED, Riddle MS, Chang C, Pimentel M. Estimating the contribution of acute gastroenteritis to the overall prevalence of irritable bowel syndrome. *J Neurogastroenterol Motil*. 2012;18(2):200-204.
20. Wensaas KA, Langeland N, Hanevik K, Morch K, Eide GE, Rortveit G. Irritable bowel syndrome and chronic fatigue 3 years after acute giardiasis: historic cohort study. *Gut*. 2012;61(2):214-219.
21. Marshall JK, Thabane M, Garg AX, Clark WF, Salvadori M, Collins SM. Incidence and

epidemiology of irritable bowel syndrome after a large waterborne outbreak of bacterial dysentery. *Gastroenterology.* 2006;131(2):445-450; quiz 660.
22. Pimentel M, Lembo A. Microbiome and its role in irritable bowel syndrome. *Dig Dis Sci.* 2020;65(3):829-839.
23. Dionne J, Ford AC, Yuan Y, et al. A systematic review and meta-analysis evaluating the efficacy of a gluten-free diet and a low FODMAPs diet in treating symptoms of irritable bowel syndrome. *Am J Gastroenterol.* 2018;113(9):1290-1300.
24. Skodje GI, Sarna VK, Minelle IH, et al. Fructan, rather than gluten, induces symptoms in patients with self-reported non-celiac gluten sensitivity. *Gastroenterology.* 2018;154(3):529-539.e522.
25. Hill C, Guarner F, Reid G, et al. Expert consensus document. The International Scientific Association for Probiotics and Prebiotics consensus statement on the scope and appropriate use of the term probiotic. *Nat Rev Gastroenterol Hepatol.* 2014;11(8):506-514.
26. Ford AC, Harris LA, Lacy BE, Quigley EMM, Moayyedi P. Systematic review with meta-analysis: the efficacy of prebiotics, probiotics, synbiotics and antibiotics in irritable bowel syndrome. *Aliment Pharmacol Ther.* 2018;48(10):1044-1060.
27. Pimentel M, Lembo A, Chey WD, et al. Rifaximin therapy for patients with irritable bowel syndrome without constipation. *N Engl J Med.* 2011;364(1):22-32.
28. 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.
29. Lembo AJ, Lacy BE, Zuckerman MJ, et al. Eluxadoline for irritable bowel syndrome with diarrhea. *N Engl J Med.* 2016;374(3):242-253.
30. Cash BD, Lacy BE, Schoenfeld PS, Dove LS, Covington PS. Safety of eluxadoline in patients with IBS-D without a gallbladder. *Am J Gastroenterol.* 2017;112(10):1619-1620.
31. Ford AC, Brandt LJ, Young C, Chey WD, Foxx-Orenstein AE, Moayyedi P. Efficacy of 5-HT3 antagonists and 5-HT4 agonists in irritable bowel syndrome: systematic review and meta-analysis. *Am J Gastroenterol.* 2009;104(7):1831-1843; quiz 1844.
32. Lacy BE, Nicandro JP, Chuang E, Earnest DL. Alosetron use in clinical practice: significant improvement in irritable bowel syndrome symptoms evaluated using the US Food and Drug Administration composite endpoint. *Therap Adv Gastroenterol.* 2018;11:1756284818771674.
33. Lacy BE. Review article: an analysis of safety profiles of treatments for diarrhoea-predominant irritable bowel syndrome. *Aliment Pharmacol Ther.* 2018;48(8):817-830.