Individualizing Pharmacologic Management of Irritable Bowel Syndrome

Louis Kuritzky, MD

CONTINUING MEDICAL EDUCATION

LEARNING OBJECTIVES:

1. Characterize the scope of problem in primary care
2. Implement recommended strategies for diagnostic testing
3. Compare the benefits and limitations of non-pharmacologic and pharmacologic therapy
4. Select evidence-based treatment

TARGET AUDIENCE

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

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Louis Kuritzky, MD, Clinical Assistant Professor Emeritus, Department of Community Health and Family Medicine, College of Medicine, University of Florida, Gainesville, FL

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CASE STUDY. FB is a 31-year-old female who called the previous day for an appointment with her primary care physician (PCP). The PCP greets FB and says, "You were here 2 weeks ago for a follow-up visit for your asthma. Everything seemed to be okay then. Have you been having difficulties since I saw you?"

FB says "No, my asthma symptoms have been okay. I've wanted to talk with you for some time about something else. I've been having problems going to the bathroom, but there never seems to be time to discuss this when I see you. I just want these problems to go away."

INTRODUCTION

Epidemiology

The emotions expressed by this patient are not uncommon in patients with irritable bowel syndrome (IBS), whether their symptoms are constipation predominant IBS (IBS-C), diarrhea-predominant IBS (IBS-D), or mixed (IBS-M).[1,2] A recent survey of people with mild/moderate IBS asked: "What is the most important thing your health care provider can do to maximize his/her relationship with you?" The topmost issue participants identified was, "I need more empathy and listening from my health care provider about how much IBS affects my life."[3]

The prevalence of IBS varies widely by geographic region and diagnostic criteria. The syndrome affects an estimated 12% of people in North America, with women at higher risk than men (relative risk 1.67).[4] IBS-D is the most common subtype of IBS (40% of diagnoses), compared with IBS-C (35%) and IBS-M (23%).[4] Comorbidities of IBS include pain hypersensitivity syndromes such as fibromyalgia, interstitial cystitis, migraine, chronic pelvic pain, and temporomandibular joint disorders.[5,6] IBS is associated with reduced work productivity and increased use of health-related resources.[7,8]

People with IBS experience significant morbidity, including lower self-esteem and overall poorer psychologic quality of life.[6] Physical quality of life has been reported to be the same as or worse than patients with diabetes, depression, or gastroesophageal reflux disease.[9] It has been reported that on average, people with IBS would sacrifice 10 to 15 years of their remaining life expectancy for an immediate cure.[10] IBS generally affects men and women similarly, although women may experience slightly greater severity of somatic symptoms and lower quality of life, the latter due to greater anxiety.[11,12] Women with IBS-D are particularly bothered by social concerns, and may resort to procedures like altering clothing, avoiding strenuous exercise, and avoiding activities they think might place them at risk of embarrassment (eg, having to frequently use the toilet during a long trip).[12]

DIAGNOSIS

The ill-defined pathogenesis of IBS, lack of a biomarker for the disease, and no universally agreed definition can make diagnosis challenging. Nonetheless, IBS is not a diagnosis of exclusion and is based on the signs and symptoms consistent with ROME III criteria, and the absence of signs indicative of other abdominal pathology.

A detailed history is the most important component of diagnosis. Physical examination is oriented to exclude other pathologies that could produce similar symptoms. When choosing therapy, it is critical to identify whether constipation, diarrhea, or mixed altered stool patterns predominate. The course of IBS is unpredictable since 35% to 50% of patients will demonstrate a chronically stable condition, other patients completely remit, and still others fluctuate between IBS categories and severity of symptoms.[13]

One widely recognized standard for the diagnosis of IBS is the Rome III criteria.[14] According to Rome III, IBS is defined by the presence of recurrent abdominal pain or discomfort at least 3 days/month in the past 3 months associated with 2 or more of the following:

- Improvement with defecation
- Onset associated with a change in frequency of stool
- Onset associated with a change in form (appearance) of stool.

To satisfy the Rome III criteria, symptom onset should occur at least 6 months before diagnosis.[15]

Patients for whom diagnostic testing is appropriate are those with alarm features such as age at onset older than 50 years, systemic signs (eg, unintentional weight loss, fever), nocturnal symptoms, family history of colon cancer, and any sign of bleeding (eg, anemia, rectal bleeding, positive fecal occult blood test, hematemesis). Symptoms of IBS-D and recent antibiotic use should prompt evaluation for *Clostridium difficile* colitis.[16] In the absence of alarm features, diagnostic testing provides no additional diagnostic certainty.[16-20] However, some experts recommend the performance of selected tests, such as complete blood count, C-reactive protein or fecal calprotectin, serologic testing for celiac disease, and age-appropriate screening for colorectal cancer, to exclude other organic diseases.[21]

Abdominal symptoms (eg, pain, discomfort, cramping, bloating) more commonly prompt patients to seek medical care than altered bowel habits (eg, urgency, loose/watery stools, frequency, straining).[22] The frequency and severity of bloating are similar or greater in people with IBS-C than IBS-D.[23,24] Individuals with IBS-D experience a greater decline in quality of life—they are more likely to alter their food intake and experience greater impact on daily activities and

TABLE 1 Summary of initial interventions for IBS[27]

Statement	Strength of recommendation	Quality of evidence
Specialized diets may improve symptoms in individual IBS patients.	Weak	Very low
Fiber provides overall symptom relief in IBS.	Weak	Moderate
Psyllium, but not bran, provides overall symptom relief in IBS (data presented for psyllium).	Weak	Moderate
There is no evidence that polyethylene glycol improves overall symptoms and pain in patients with IBS.	Weak	Very low
Certain antispasmodics provide symptomatic short-term relief in IBS. Adverse events are more common with antispasmodics than placebo.	Weak	Low
There is insufficient evidence to recommend loperamide for use in IBS.	Strong	Very low
There is insufficient evidence to recommend prebiotics or synbiotics in IBS.	Weak	Very low
Taken as a whole, probiotics improve global symptoms, bloating, and flatulence in IBS. Recommendations regarding individual species, preparations, or strains cannot be made at this time because of insufficient and conflicting data.	Weak	Low
Peppermint oil is superior to placebo in improving IBS symptoms. The risk of adverse events is no greater with peppermint oil than with placebo.	Weak	Moderate
A variety of psychological interventions are effective in improving IBS symptoms.	Weak	Very low

Abbreviations: IBS, irritable bowel syndrome.

relationships than those with IBS-C.[25] Bloating negatively impacts energy level and food intake, the latter particularly among women.[12,22] Compared with persons with minimal or mild bloating, persons with IBS and moderate to severe bloating report more daily symptoms of anxiety and depression, have more history of depressive disorders, and exhibit higher psychological distress.[26]

CASE STUDY (CONTINUED). The history shows that FB's bowel habits changed nearly 2 years ago when she began to experience abdominal bloating and occasional diarrhea. Since that time, her symptoms have increased and she now has abdominal discomfort 3 to 4 days per month. The pain is usually relieved with defecation. The frequency of her bowel movements has changed, and she now has more than 1 bowel movement on some days. FB also notes that she occasionally won't have a bowel movement for 3 to 4 days. Because FB has no alarm features for IBS, her PCP decides no further work-up is needed and makes a diagnosis of IBS-D based upon Rome III criteria.

TREATMENT

The overall management of a person with IBS emphasizes the importance of safety since IBS is not a fatal disease. However, because quality of life can be dramatically reduced, identifying and treating the symptoms that are most concerning to the patient is also a high priority.

CASE STUDY (CONTINUED). The PCP discusses some of the possible causes of IBS-D and asks her to review *IBS: A patient's guide to living with irritable bowel syndrome*, which was developed by the American Gastroenterological Association (www.gastro.org/patient-center/IBS_Brochure_Online.pdf).

The PCP assures FB that there are many treatment options for IBS and would like to begin with treatments that pose minimal safety concerns. She refers FB to a website that discusses low FODMAP (fermentable oligo-di-monosaccharides and polyols) diets to help her identify foods that might be causing her symptoms and to avoid or reduce eating those foods. FB is also advised to use an over-the-counter antidiarrheal, such as loperamide, for more severe symptoms. They also talk about situations that may be particularly stressful and how to handle them.

Initial therapy

Patients with IBS are frequently treated initially with self-care and other nonprescription interventions. While many of these treatments are supported by weak evidence, their safety supports their use as initial therapy (**TABLE 1**).[27-29] Soluble fiber (psyllium) appears to be more beneficial than insoluble fiber

TABLE 2 Key safety considerations with selected prescription medications for IBS

Medication (IBS subtype)	Contraindications	Warnings/pregnancy	Common adverse events
Lubiprostone[35] (women age ≥18 y with IBS-C)	• Known or suspected mechanical GI obstruction	• Avoid in severe diarrhea • Pregnancy category C	• Nausea • Diarrhea • Abdominal pain
Linaclotide[36] (IBS-C)	• Children ages <6 years • Known or suspected mechanical GI obstruction	• Avoid in children age 6-17 years • Pregnancy category C	• Diarrhea • Abdominal pain • Flatulence • Abdominal distension
Rifaximin[37] (IBS-D)	• History of hypersensitivity to rifaximin or rifamycin antimicrobial agents	• May cause *Clostridium difficile*-associated diarrhea • Caution in hepatic impairment (Child-Pugh Class C) • Avoid concomitant use with a P-glycoprotein inhibitor • Pregnancy category: Not categorized	• Increased alanine aminotransferase • Nausea
Eluxadoline[38] (IBS-D)	• Known or suspected biliary duct obstruction • Sphincter of Oddi disease or dysfunction • Alcohol abuse, drinks >3 alcoholic beverages/day • Pancreatitis, structural disease of pancreas • Hepatic impairment (Child-Pugh Class C) • Severe constipation or sequelae from constipation or known or suspected mechanical GI obstruction	• Sphincter of Oddi spasm and pancreatitis • Pregnancy category: Not categorized	• Constipation • Nausea • Abdominal pain
Alosetron[39] (Women with severe IBS-D)	• History of chronic or severe constipation or sequelae from constipation; intestinal obstruction, stricture, toxic megacolon, GI perforation, and/or adhesions; ischemic colitis; impaired intestinal circulation, thrombophlebitis, or hypercoagulable state; Crohn's disease or ulcerative colitis; diverticulitis; severe hepatic impairment • Concomitant use of fluvoxamine	• Infrequent GI AEs, eg., ischemic colitis and serious complications of constipation • Pregnancy category B	• Constipation • Abdominal discomfort and pain • Nausea • GI discomfort and pain

Abbreviations: AEs, adverse events; GI, gastrointestinal; IBS, irritable bowel syndrome; IBS-C, constipation-predominant IBS; IBS-D, diarrhea-predominant IBS.

(bran) in symptom improvement for all IBS, but may worsen bloating. Nonprescription medications for initial therapy include diphenoxylate/atropine and loperamide or other anticholinergics for IBS-D, and bisacodyl, docusate sodium, lactulose, polyethylene glycol 3350 for IBS-C.

A variety of psychological interventions, including cognitive behavioral therapy, have shown favorable results, and should be considered in patients who prefer such modalities or who do not respond to initial pharmacologic treatments.[30] The use of probiotics for IBS is supported by some evidence, generally showing benefit in improving overall symptoms and reducing abdominal pain, bloating, and flatulence. Benefits were primarily observed for combination products rather than individual probiotics.[31-34]

CASE STUDY (CONTINUED). At a 2-month follow-up, FB tells her PCP that she used a FODMAP reference to identify some foods to avoid and tracked her diet and symptoms since her last visit. She tried loperamide and reports less bloating as well as reduced stool frequency. She now experiences fewer days with more than 1 bowel movement and her pain and bloating are less severe.

FB and her PCP discuss further modifications to her diet and lifestyle. When her physician suggests psychological counseling, FB declines referral and asks if there is a medication that would help her.

Prescription medications

Prescription medications are second-line therapy in patients

TABLE 3 Summary of prescription medications for IBS[27]

Statement	Strength of recommendation	Quality of evidence
Alosetron is effective in females with IBS-D.	Weak	Moderate
Linaclotide is superior to placebo for the treatment of IBS-C.	Strong	High
Lubiprostone is superior to placebo for the treatment of IBS-C.	Strong	Moderate
Rifaximin is effective in reducing total IBS symptoms and bloating in IBS-D.	Weak	Moderate
Antidepressants (tricyclic antidepressants and SSRIs) are effective in symptom relief in IBS. Side effects are common and may limit patient tolerance.	Weak	High
Mixed 5-HT4 agonists/5-HT3 antagonists are not more effective than placebo at improving symptoms of IBS-C.	Strong	Low

Abbreviations: 5-HT3, serotonin subtype 3; 5-HT4, serotonin subtype 4; IBS, irritable bowel syndrome; IBS-C, constipation-predominant IBS; IBS-D, diarrhea-predominant IBS; SSRI, selective serotonin reuptake inhibitor.

who do not achieve adequate relief of the predominant symptoms of IBS with initial therapy (eg, bloating, abdominal pain, constipation, diarrhea).[1] Safety remains a key consideration in selecting therapy (**TABLE 2,** previous page).[35-39] In addition to safety, treatment selection is guided by factors such as patient comorbidities, values, and preferences, as well as medication cost and insurance coverage. Since there are few high-quality, head-to-head studies, recommending a treatment hierarchy is difficult. Treatment selection may also be guided by the strength of recommendation and quality of evidence from a 2014 meta-analysis conducted by the American College of Gastroenterology (**TABLE 3**).[27]

The 2 newest prescription medications for IBS are rifaximin and eluxadoline, both approved by the FDA in May 2015. Rifaximin is a derivative of the antibacterial rifampin.[37] Gastrointestinal absorption of both eluxadoline and rifaximin is minimal.[37,38] Eluxadoline is a mu-opioid receptor agonist, as well as a delta-opioid receptor antagonist and a kappa-opioid receptor agonist.[38] A brief overview of these less familiar medications is provided below.

Rifaximin

The safety and efficacy of rifaximin for the treatment of IBS-D were established in 3 double-blind, placebo-controlled trials. The 2 TARGET trials utilized identical designs in which a total of 1258 patients with IBS, but excluding IBS-C, were randomly assigned to receive rifaximin 550 mg or placebo 3 times daily for 14 days.[40] Patients were then followed for an additional 10 weeks without further treatment. Every 2 weeks of the 12-week study, patients were asked if they had adequate relief of their IBS symptoms during the previous 7 days. Significantly more patients treated with rifaximin than placebo answered "yes" for at least 2 of the first 4 weeks after treatment (40.8% vs 31.2%, respectively, *P*=.01 in TARGET 1; 40.6% vs 32.2%, respectively, *P*=.03 in TARGET 2). Similarly, significantly more patients treated with rifaximin than placebo: (1) achieved adequate relief of IBS-related bloating for at least 2 of the first 4 weeks after treatment; (2) had relief of IBS-related abdominal pain and discomfort during the primary evaluation period; and (3) had adequate relief of global IBS symptoms within the first month, with continued relief during the first 2 months and during all 3 months in both studies. Over the 12 weeks, the incidences of adverse events and serious adverse events were similar in the rifaximin and placebo groups.

A third study evaluated repeat treatment for up to 46 weeks.[37] The first phase was a 14-day open-label period, with responders followed for up to 20 treatment-free weeks. Responders had defined improvements in weekly average abdominal pain scores and stool consistency. Those who experienced a recurrence were randomized to rifaximin 550 mg or placebo three times per day (N=636) for two additional 14-day repeat treatment courses separated by 10 weeks. More patients treated with rifaximin than placebo were responders (reduced abdominal pain and improved stool consistency) in this final phase of the study.[37]

Eluxadoline

Two clinical trials of eluxadoline included a total of 2425 patients who met Rome III criteria for IBS-D with abdominal pain >3.0/10 and daily stool consistency score (Bristol Stool Scale) ≥5.5 and ≥5 on at least 5 days during the week prior to randomization.[38] Both clinical trials lasted 26 weeks; one had a 26-week extension followed by a 2-week follow-up, while the other included a 4-week placebo-withdrawal period following completion of the 26 weeks. Patients were randomized to 75 or 100 mg of eluxadoline or placebo twice daily. Efficacy was evaluated using an overall composite responder endpoint (simultaneous improvement of worst abdominal

pain by ≥30% and Bristol Stool Score <5 on the same day for ≥50% of days over the interval).[38]

In both studies, the proportion of patients who were composite responders to eluxadoline over 12 weeks was significantly higher compared with placebo for both doses. The proportion did not differ by sex. The composite response rates over 26 weeks were similar to placebo. During the 4-week withdrawal period in the second study, no evidence of worsening diarrhea or abdominal pain compared to baseline was demonstrated at either dose.[38]

SUMMARY

Irritable bowel syndrome is a common gastrointestinal disorder with constipation, diarrhea, and mixed subtypes. The diagnosis is generally based on a detailed history utilizing the Rome III criteria. Alarm signals necessitate more extensive diagnostic evaluation. Nonpharmacologic options and over-the-counter remedies (eg, loperamide) might not be supported by strong evidence, but are often chosen as initial treatment for their safety and tolerability. Psychological interventions may be beneficial. Newer pharmacologic agents such as alosetron, eluxadoline, linaclotide, lubiprostone, and rifaximin are supported by higher quality evidence than older agents such as antispasmodics and laxatives.

Patients with IBS commonly report that clinicians offer insufficient empathy and validation of their symptoms. Physicians therefore should strive to improve communication methods that specifically provide such reassurance. Individualizing treatment based on patient values and preferences is essential. ●

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