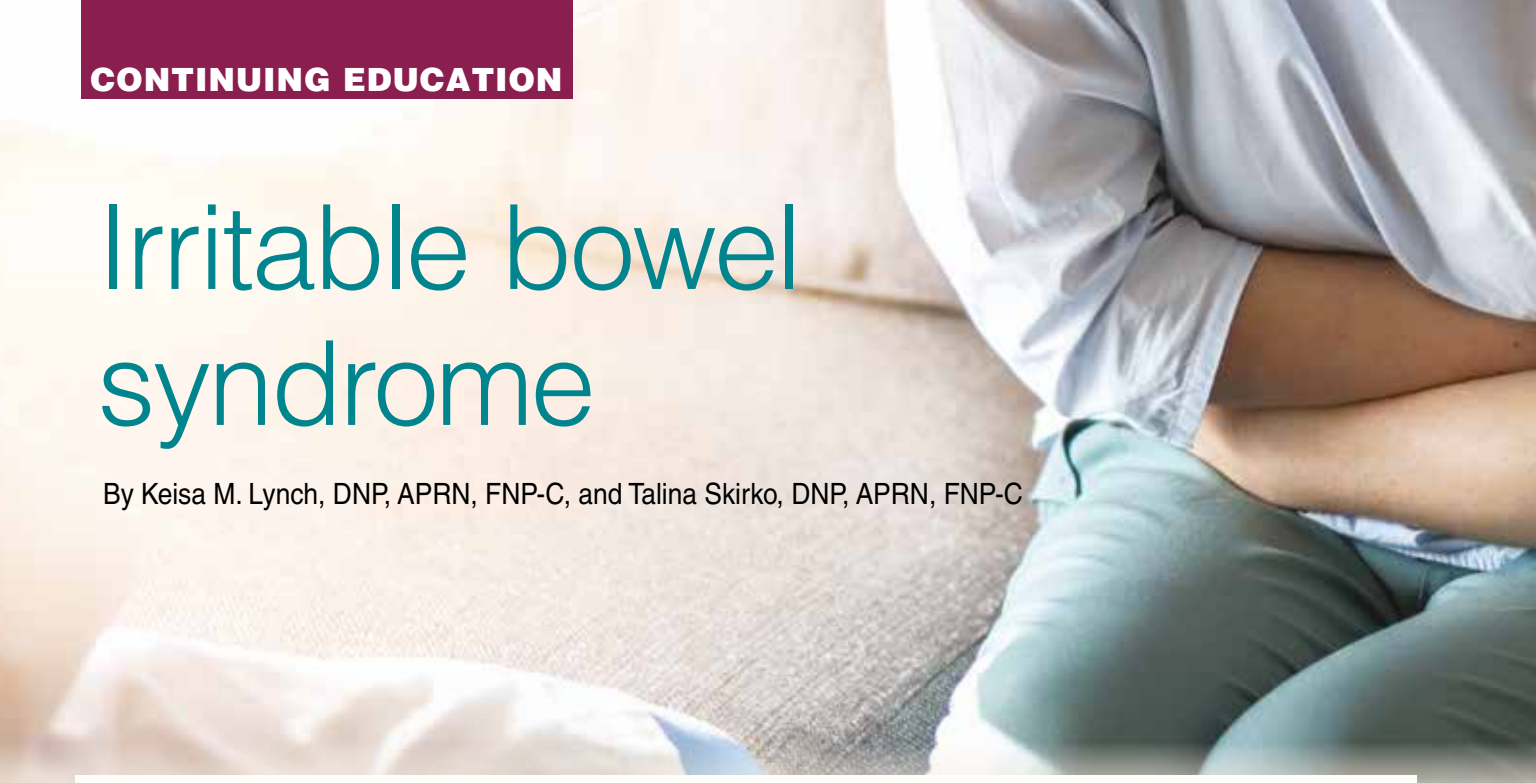

Irritable bowel syndrome

By Keisa M. Lynch, DNP, APRN, FNP-C, and Talina Skirko, DNP, APRN, FNP-C

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Intended audience: This continuing education (CE) activity has been designed to meet the educational needs of nurse practitioners and other healthcare providers who provide primary care for women.

CE approval period: Now through August 31, 2023

Estimated time to complete this activity: 1 hour

CE approval hours: 1.0 contact hour of CE credit including 0.50 contact hours of pharmacology content

Goal statement: Nurse practitioners and other healthcare providers who provide primary care for women will increase their knowledge about the assessment, diagnosis, and treatment of irritable bowel syndrome.

Needs assessment: Irritable bowel syndrome (IBS) is the most common functional gastrointestinal (GI) disease, with prevalence in the United States estimated at 14% among women. IBS is often associated with other functional GI conditions as well as non-GI syndromes such as fibromyalgia, chronic pelvic pain, migraine, and depression and anxiety. IBS can have a significant effect on quality of life, interrupting many activities of daily living. Knowledge about signs and symptoms, differential diagnosis, and both nonpharmacologic and pharmacologic management is needed to help individuals effectively manage symptoms, improve quality of life, and reduce the economic burden of IBS.

Educational objectives: At the conclusion of this educational activity, participants should be able to:

1. Identify the criteria for the diagnosis of IBS.
2. Discuss dietary alterations, cognitive behavioral therapy, and other psychotherapy as components in the management of IBS.
3. Describe mechanism of action, factors that influence specific drug choice, patient education on use, adverse effects, and contraindications for pharmacologic options in treating IBS.

Accreditation statement: This activity has been evaluated and approved by the Continuing Education Approval Program of the National Association of Nurse Practitioners in Women's Health (NPWH) and has been approved for 1 contact hour CE credit, including 0.50 hours of pharmacology credit.

Faculty disclosures: NPWH policy requires all faculty to disclose any affiliation or relationship with a commercial interest that may cause potential, real, or apparent conflict of interest with the content of a CE program. NPWH does not imply that affiliation or relationship will affect the content of the CE program. Disclosure provides participants with information that may be important to their evaluation of an activity.

Keisa M. Lynch, DNP, APRN, FNP-C, has no actual or potential conflicts of interest in relation to the contents of this article. **Talina Skirko, DNP, APRN, FNP-C,** has no actual or potential conflicts of interest in relation to the contents of this article.

Disclosure of unlabeled/unapproved use: NPWH policy requires authors to disclose to participants when they are presenting information about unlabeled use of a commercial product or device or an investigational use of a drug or device not yet approved for any use.

Disclaimer: Participating faculty members determine the editorial content of the CE activity; this content does not necessarily represent the views of NPWH. This content has undergone a blinded peer review process for validation of clinical content. Although every effort has been made to ensure that the information is accurate, clinicians are responsible for evaluating this information in relation to generally accepted standards in their own communities and integrating the information in this activity with that of established recommendations of other authorities, national guidelines, FDA-approved package inserts, and individual patient characteristics.

To participate in this CE program, click *here*[A].

Successful completion of the activity: Successful completion of this activity, J-21-04, requires participants to do the following:

1. "Sign In" in at the top right-hand corner of the page npwh.org/courses/home/details/1633 if you have an NPWH account. You must be signed in to receive credit for this course. If you do not remember your username or password, please follow the "Forgot Password" link and instructions on the sign in page. If you do not have an account, please click on "Create an Account."*
2. Read the learning objectives, disclosures, and disclaimers on the next page and then click on the "Continue" button.
3. Study the material in the learning activity during the approval period (now through August 31, 2023).
4. Complete the post-test and evaluation. You must earn a score of 70% or higher on the post-test to receive CE credit.
5. Print out the CE certificate after you have successfully passed the post-test and completed the evaluation.

*If you are an NPWH member, were once a member, or have completed CE activities with NPWH in the past, you have a username and password in our system. Please do not create a new account. Creation of multiple accounts could result in loss of CE credits as well as other NPWH services. If you do not remember your username or password, either click on the "Forgot Username" or "Forgot Password" link or call the NPWH office at (202) 543-9693, ext. 1.

Commercial support: This activity did not receive any commercial support.

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Irritable bowel syndrome (IBS) is the most common functional gastrointestinal (GI) disease with a pooled high global prevalence estimated at 11.2%. The national prevalence is estimated at 10% to 12%, with some estimates as high as 21%, and IBS more commonly affects women. Other IBS-associated disorders are often related to additional GI diseases such as functional dyspepsia, nausea, heartburn, and gastroesophageal reflux disease, as well as incontinence and pelvic floor dyssynergia. IBS is a very important healthcare concern given its high prevalence, the effects it has on quality of life, and the significant economic burden to the healthcare system.

KEY WORDS: **irritable bowel syndrome, functional gastrointestinal disease, IBS, nurse practitioner, pharmacologic treatment, IBS treatment**

Irritable bowel syndrome (IBS) is the most common functional gastrointestinal (GI) disease, with a pooled high global prevalence estimated at 11.2%. Prevalence in the United States is estimated at 10% to 12%, with some estimates as high as 21%. IBS is more common in women than in men (14% compared with 8.9% for males). IBS is more common in lower socioeconomic groups and is more commonly diagnosed in patients younger than age 50 years.[1-4]

Individuals with IBS experience recurrent abdominal pain that is associated with defecation or a change in bowel habits. They typically have constipation, diarrhea, or mix of constipation and diarrhea. Symptoms of abdominal bloating/distension are common. GI conditions such as functional dyspepsia, nausea, heartburn, gastroesophageal reflux disease, fecal incontinence, and failure of pelvic floor muscles to relax with defection (dyssynergia) are often associated with IBS.[5] Additional non-GI syndromes have been recognized to coexist, such as asthma, fibromyalgia, chronic pelvic pain, interstitial cystitis, migraine, chronic fatigue syndrome, depression, and anxiety.[6–10] IBS is a very important healthcare concern given its high prevalence, the effects it has on health-related quality of life (HRQOL), as well as the significant economic burden it poses to the healthcare system. Individuals with IBS often report high rates of psychopathology and low quality of life, avoiding daily activities such as work/school, exercise, sexual intercourse, household chores, socializing, travel, and eating.[11]

The significant economic burden of IBS is related to the direct (healthcare) and indirect (missed days from work) costs. Each year in the United States, IBS accounts for nearly 3.1 million ambulatory care visits and 5.9 million prescriptions, with total direct and indirect costs exceeding $20 billion.[2]

This article describes steps the nurse practitioner (NP) in a primary care setting can take to make an accurate diagnosis of IBS, limit unnecessary invasive diagnostic testing, and develop effective treatment plans that are optimal for improving HRQOL and reducing the economic burden of this disease.

Pathophysiology

The pathophysiology of IBS is most

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likely multifactorial and not completely understood.[6] Traditionally, IBS research aimed to explore the underlying mechanism of IBS with alterations of GI motility and visceral sensory function. Subsequent research, however, has shifted its focus to exploring other possibilities of brain-gut axis; diet; genetic factors; infections and disturbances in the microbiota; low-grade mucosal inflammation, immune activation and altered intestinal permeability; disordered bile salt metabolism; abnormalities in serotonin metabolism; and alterations in brain function.[6]

Assessment and diagnosis

The diagnosis of IBS is made by obtaining a careful history, performing a focused physical examination, and obtaining limited laboratory tests. Diagnosis relies primarily on symptom-based criteria, with no alarm features (symptom onset > age 50 years, recent change in bowel habits, unintentional weight loss, family history of colon cancer or inflammatory bowel disease (IBD), nocturnal passage of stools, overt GI bleeding, and unexplained iron-deficiency anemia) and is a diagnosis of exclusion of other organic diseases.

The symptom-based Rome IV criteria is the gold standard used for the diagnosis of IBS. Rome criteria were first established in 1984 and have evolved over time to the current Rome IV version in 2016. The Rome IV criteria for a diagnosis of IBS include recurrent abdominal pain on average of at least 1 day/week that is associated with two or more of the following: related to defecation, change in frequency of stool, change in form/appearance of stool. Disordered bowel habits are typically present (ie, constipation, diarrhea, or mix of constipation and diarrhea) as are symptoms of abdominal bloating/distension. Symptom onset should occur at least 6 months prior to diagnosis, and symptoms should be present during the last 3 months.[12]

Normal abdominal and rectal exam findings further support the diagnosis of IBS as well as providing the patient with reassurance. Significant abdominal or rectal tenderness or masses, lymphadenopathy, and/or blood in stool found on physical exam warrant further investigation.

It is reasonable to include a complete blood count with differential and C-reactive protein (CRP), as well as a thyroid panel if clinical suspicion is high for thyroid disease in the diagnostic workup. For patients with chronic diarrhea, an evaluation for possible celiac disease is recommended, given that both diseases can share some similar GI symptoms.[13,14] Tests for celiac disease include IgA tissue transglutaminase and a second test to detect celiac disease in the setting of IgA deficiency, such as IgG tissue transglutaminase and IgG or IgA deamidated gliadin peptides.[13] A positive serologic test would warrant confirmation biopsies in the duodenum of the small bowel on an upper endoscopy before recommending a gluten-free diet.

A systematic review and meta-analysis were completed to evaluate the usefulness of laboratory testing, including CRP, erythrocyte sedimentation rate (ESR), fecal calprotectin, and lactoferrin in patients to distinguish between IBS and IBD (ie, ulcerative colitis, indeterminate colitis, Crohn's disease). It demonstrated that CRP of 0.5 mg/dL or less and fecal calprotectin less than 40 µg/g are sufficient to effectively exclude IBD.[1,15,16]

Performing investigations such as colonoscopy is usually not necessary and does not seem to improve patient satisfaction or HRQOL.[13,14] A colonoscopy should be performed when alarm features are present, or if there is high suspicion of IBD based on history taking or laboratory parameters, or for colon cancer screening. When a patient's predominant symptom is painless watery diarrhea, especially in women over age 50 years, a colonoscopy with random biopsies to rule out microscopic colitis should be considered.[17]

When the patient meets the Rome IV symptom-based criteria,

Table. Differential diagnosis for IBS

Disease	Signs/symptoms	Tests
Inflammatory bowel disease • Crohn's disease	• Diarrhea • Abdominal pain • Fever • Weight loss • Rectal bleeding	• Fecal calprotectin is typically positive • Labs: anemia, hypoalbuminemia • Upper endoscopy not routinely recommended unless upper GI symptoms are present • Colonoscopy: discontinuous distribution of longitudinal ulcers, cobblestone appearance, and aphthous ulcerations
Inflammatory bowel disease • Ulcerative colitis	• Bloody diarrhea • Diarrhea • Urgency • Tenesmus • Abdominal pain	• Fecal calprotectin is typically positive • Labs: anemia • Colonoscopy typically shows edematous mucosa, erythema, loss of vascular pattern, and mucosal friability. Erosions and ulcerations are associated with severe disease. Luminal narrowing may be noted.
Celiac sprue	• Diarrhea • Fatigue • Weight loss • Bloating/flatulence • Abdominal pain • Early onset of osteoporosis	• Labs: iron deficiency anemia • Anti-tissue transglutaminase IgA is typically elevated • Small bowel biopsy confirmatory of diagnosis
Colon cancer	• Blood in stool • Abdominal pain • Unexplained weight loss • Persistent change in stool habits or caliber	• Labs: iron deficiency anemia • Fecal immunohistochemistry stool test (FIT) – positive • Stool DNA screening test – positive • Colonoscopy – malignant growth

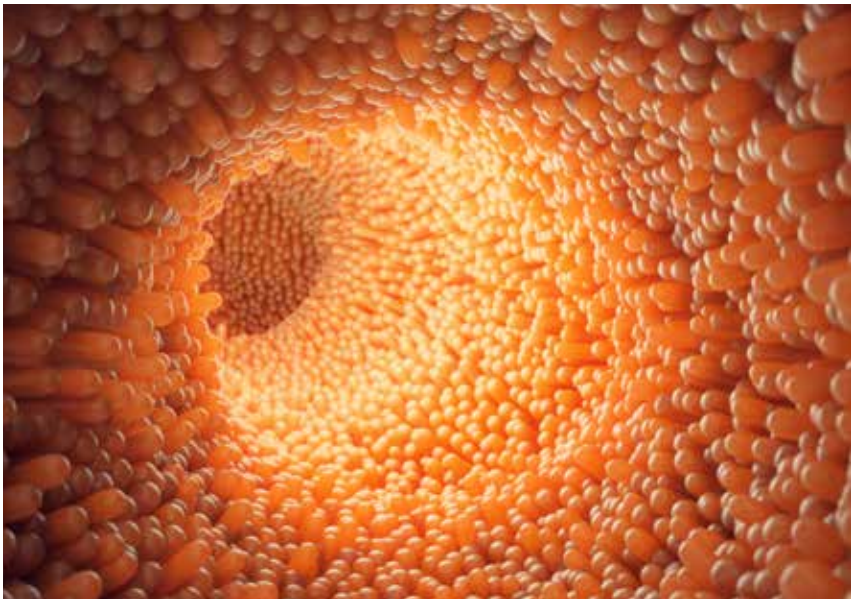
has no alarm features, and has normal physical exam and focused laboratory test findings, the provider can make the diagnosis of IBS. Because IBS is considered a diagnosis of exclusion of other organic diseases, the provider conducts the assessment with an awareness that symptoms of IBS can appear in other disease conditions. The differential diagnosis would include the conditions listed in the *Table*.

Management

Patients with IBS typically seek care from their primary care providers driven by the severity of symptoms, HRQOL, and psychological symptoms.[17] It is crucial from the start to establish an effective patient–provider relationship, with education and reassurance as important components for IBS management. Because no cure has been identified and a substantial portion of patients will have spontaneous remission of symptoms over time, management should target the most bothersome symptoms the patient is currently experiencing. Considering the four different subtypes of IBS based on the most predominant bowel habits that exist is important to effectively focus treatment. The IBS-specific subtypes include IBS with predominant constipation (IBS-C), IBS with predominant diarrhea (IBS-D), IBS with mixed bowel habits (IBS-M), and unsubtyped IBS. Treatment includes dietary alterations, behavioral therapy and psychotherapy, and pharmacotherapy.

Dietary alterations are potential treatment strategies for all subtypes.[6] According to a recent US survey of GI specialists (N = 1,562), IBS patients commonly first use a trial-and-error dietary approach to manage GI symptoms, followed by a lactose-free and gluten-free diet, and rarely use a low, fermentable oligosaccharides, disaccharides, monosaccharides, and polysaccharides (FODMAP) diet on their own. Over half of GI specialists who completed the survey reported they recommend diet therapy to more than 75% of IBS patients and most commonly recommend a low FODMAP diet.[18]

The low FODMAP diet excludes several food types to which the patient may be intolerant. The results of randomized controlled trials (RCTs) on the efficacy of a low FODMAP diet are mixed, although evidence supports a possible overall benefit for about half of IBS sufferers.[19] Less data are available for the efficacy of gluten-free and other exclusion diets.[1] Based on evidence



rated as very low quality, the American College of Gastroenterology (ACG) makes a weak recommendation for use of a low FODMAP diet and against the use of a gluten-free diet or exclusion diets based on antibody or leukocyte activation tests.

The ACG does strongly recommend the use of soluble fiber in patients with IBS (eg, psyllium, methylcellulose, calcium polycarbophil supplements) for overall symptom improvement based on evidence rated as moderate quality. Insoluble fiber (eg, wheat, corn, or bran) is not recommended as it may exacerbate pain and bloating with no evidence of efficacy in symptom improvement.[1]

The concept that alterations in the gut microbiome might be relevant to IBS has led to the use of interventions to modify the microbiota such as probiotics. Probiotics are live microorganisms, the most common being bacteria found in the *Lactobacillus* and *Bifidobacterium* group.[20]

The ACG notes there are some data to support the use of probiotics to improve global symptoms as well as bloating and flatulence in IBS.[1] There are a myriad of probiotics available over the counter (OTC), each of which claim specific advantages over the others. The studies examining probiotics in IBS are limited, as they usually only include single- or multi-organism cocktails and are typically conducted at small centers. Further research on the use of probiotics in patients with IBS is important given that alterations in the intestinal microbiome might be significant.[21]

Peppermint oil has several mechanisms of action, some of which may benefit the patient with IBS, including GI smooth muscle relaxation, by reducing calcium influx; visceral hypersensitivity modulation; antimicrobial effects; anti-inflammatory activity; and modulation of psychosocial distress. Overall, the most common adverse effect noted is heartburn, although it appears to be no more common in peppermint oil than placebo. This adverse effect is presumably related to its effect as a relaxant of esophageal muscle. It may be avoided using enteric-coated preparation of peppermint oil that would provide more distal delivery.[22]

The high prevalence of psychiatric comorbidities such as anxiety and depression have been implicated in both the causation as well as the severity of IBS. Recognition and treatment of these comorbidities is crucial to improve overall HRQOL.[23] A variety of psychological interventions have been efficacious in improving IBS symptoms, including cognitive behavioral therapy (CBT), hypnotherapy, multicomponent psychotherapy, and dynamic psychotherapy.[2,24]

Although bowel movements are more frequent and colonic transit is more rapid in individuals who are more physically active than in sedentary individuals, it is not clear if exercise leads to overall symptom improvement in patients with IBS.[25] A meta-analysis of various forms of exercise suggests that exercise had significant benefits for patients with IBS but that studies were limited by the strong risk of bias.[25] The ACG guidelines provide a weak recommendation for exercise as management for overall symptom improvement in IBS, as based on limited data and only a few well-designed clinical studies to date.[1]

Pharmacologic therapy

Pharmacologic therapy can be an important component in the management of IBS when non-pharmacologic treatments alone are not effective. Antidiarrheals for IBS-D, laxatives for IBS-C, and antispasmodics for abdominal pain are the initial pharmacologic treatment strategies. US Food and Drug Administration (FDA)-approved medications are available for both IBS-D and IBS-C. None of the medications discussed here have been thoroughly studied for use in pregnancy and lactation. The NP should use caution and consider consultation with a GI specialist regarding continuing use if the patient becomes pregnant or is lactating.

The ACG guidelines provide a weak recommendation for certain

antispasmodic treatments such as otilonium, pinaverium, hyoscyamine, cimetropium, drotaverine, and dicyclomine for overall symptom improvement in IBS. The evidence to support their use is modest, although they may exert short-term benefits. The most common side effects are dry mouth, dizziness, and blurred vision, but no serious adverse events have been reported with these treatment options.[1] Currently, three pharmacologic agents have received FDA approval for the treatment of IBS-D including eluxadoline, alosetron, and rifaximin.[26] Each has a different mechanism of action and variable precautions for use.

Eluxadoline, a mixed μ- and κ-opioid receptor agonist/δ-opioid antagonist, targets the opioid receptors in the GI tract and is indicated as a daily therapy for treatment of IBS-D. Three clinical trials have noted modest improvement in diarrhea and no clear effect on abdominal pain.[1] Eluxadoline should not be used in patients post cholecystectomy or who have sphincter of Oddi problems, excessive alcohol use, or other pancreatic or biliary risk factors. The most commonly reported side effects are constipation, nausea, and abdominal pain.[27,28]

Alosetron is a selective serotonin 5-HT3 antagonist. The targeted action of this drug in the intestines reduces nausea, bloating, and pain and increases bowel transit time. Alosetron has the most restricted indication of the three FDA-approved treatment options for IBS-D because of potential to cause severe constipation and ischemic colitis. It is only approved for use in women who have severe IBS-D that has failed conventional therapy and requires a prescription under an FDA-modified Risk Evaluation and Mitigation Strategy (REMS) program.[29]

A multidisciplinary approach to treating patients with IBS is becoming standard practice. This multidisciplinary team includes NPs along with other primary care providers, behavioral health (psychologists, psychiatrists, psychiatric-mental health nurse practitioners), and dieticians.

Rifaximin is an antibiotic that is not systemically absorbed and is widely believed to modulate the gut microbiota. Its efficacy and safety for short-term (2 to 3 weeks) use have been demonstrated in randomized, placebo-controlled studies in adults with IBS-D. No serious adverse events have been noted nor any clinically relevant microbial resistance.[30]

Bile acid sequestrants can be used to treat bile acid diarrhea, which may be a cause or a consequence of IBS related to excessive production or decreased absorption of bile acids influencing bowel habit and colonic transit time.[31] It is reasonable to use an empiric trial of a bile acid sequestrant, such as colestipol or cholestyramine, with a clinical response suggesting excess bile acids as the cause of chronic diarrhea.[32]

The OTC antidiarrheal loperamide is a synthetic opioid that slows intestinal motility and increases absorption of water and electrolytes movement through the bowel. Loperamide was no more effective in overall IBS symptom improvement than placebo in a pooled analysis of two RCTs. Based on this evidence, ACG suggests against the use of loperamide in the treatment of patients with IBS.[1]

The three FDA-approved pharmaceutical options for treatment of patients with IBS-C are plecanatide, linaclotide, and lubiprostone. Based on current evidence, the ACG provides a recommendation in favor of the use of these drugs to improve symptoms in patients with IBS-C.[1] All three are prosecretory agents that increase chloride and bicarbonate secretion into the intestine and prevent the absorption of sodium ions, thereby increasing secretion of water into the lumen. This increase in intestinal fluid softens the stool and accelerates intestinal transit through stimulation of local receptors sensitive to stretch and distention. They are prescribed for use on a regular, daily basis.

Plecanatide is an analog of uroguanylin, a naturally occurring prosecretory intestinal hormone.[33] It is unique in the sense that its effects are limited to the proximal small bowel. Plecanatide significantly improves abdominal pain associated with IBS-C with few adverse events.[34]

Linaclotide is an intestinal

GCC-receptor activator that is prosecretory. This drug also has antinociceptive properties leading to improvement in abdominal pain. Its most common side effect is diarrhea, as reported in 20% of patients during clinical trials.[35,36]

Lubiprostone specifically activates the type 2 chloride channel in the bowel, which promotes intestinal secretions.[37] Its most common side effects are nausea and diarrhea.

Polyethylene glycol is an osmotic laxative that is not absorbed in the intestinal lumen. It has been well established in multiple RCTs to be a very efficacious treatment for constipation and is available OTC. However, its clinical effects on other IBS-C related symptoms are not supported.

Central-acting therapies such as tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs) are often used in the treatment of IBS, particularly when the patient has psychiatric comorbidities such as depression, anxiety, or somatization. They have demonstrated effectiveness in relieving pain and psychological distress related to IBS.[1] Additionally, TCAs help improve diarrhea by slowing GI transit and SSRIs improve constipation by accelerating GI transit through targeting the brain-gut axis.[38,39]

Implications for NP practice

A multidisciplinary approach to treating patients with IBS is becoming standard practice. This multidisciplinary team includes NPs along with other primary care providers, behavioral health (psychologists, psychiatrists, psychiatric-mental health nurse practitioners), and dieticians. Patients can benefit from dietician consultation for diet planning that is individualized, healthy, and helpful in reducing IBS symptoms while not being overly restrictive. Behavioral health specialists can offer a variety of psychotherapies for patients with psychological comorbidities associated with IBS. The NP in a primary care setting can implement education and counseling for lifestyle modifications and can prescribe first-line pharmacotherapeutics for patients with mild or moderate symptoms. Reassurance that IBS does not lead to cancer or IBD and that you will partner with them to implement strategies to manage symptoms has tremendous value. Follow-up is important to answer questions, continue with reassurance, and to modify therapy as needed. Patients with alarm features, unsure diagnoses, and severe or refractory symptoms should be referred to GI specialists. ■

References

1. 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.
2. Chey WD, Kurlander J, Eswaran S. Irritable bowel syndrome: a clinical review. *JAMA.* 2015;313(9):949-958.
3. Lovell RM, Ford AC. Global prevalence of and risk factors for irritable bowel syndrome: a meta-analysis. *Clin Gastroenterol Hepatol.* 2012;10:712-721.e4
4. American College of Gastroenterology Task Force on Irritable Bowel Syndrome; Brandt LJ, Chey WD, Foxx-Orenstein AE, et al. An evidence-based position statement on the management of irritable bowel syndrome. *Am J Gastroenterol.* 2009;104(suppl 1):S1-S35.
5. Holtmann GJ, Ford AC, Talley NJ. Pathophysiology of irritable bowel syndrome. *Lancet Gastroenterol Hepatol.* 2016;1(2):133-146.
6. Enck P, Aziz Q, Barbara G, et al. Irritable bowel syndrome. *Nat Rev Dis Primers.* 2016;2:16014.
7. Sperber AD, Dekel R. Irritable bowel syndrome and co-morbid gastrointestinal and extra-gastrointestinal functional syndromes. *J Neurogastroenterol Motil.* 2010;16(2):113-119.
8. Hausteiner-Wiehle C, Henningsen P. Irritable bowel syndrome: relations with functional, mental, and somatoform disorders. *World J Gastroenterol.* 2014;20(20):6024-6030.
9. Fond G, Loundou A, Hamdani N, et al. Anxiety and depression comorbidities in irritable bowel syndrome (IBS): a systematic review and meta-analysis. *Eur Arch Psychiatry Clin Neurosci.* 2014;264(8):651-660.
10. Shen TC, Lin CL, Wei CC, et al. Bidirectional association between asthma and irritable bowel syndrome: two population-based retrospective cohort studies. *PLoS One.* 2016;11(4):e0153911.
11. Ballou S, Keefer L. The impact of irritable bowel syndrome on daily functioning: characterizing and understanding daily consequences of IBS. *Neurogastroenterol Motil.* 2017;29(4):e12982.
12. Lacy BE, Patel NK. Rome criteria and a diagnostic approach to irritable bowel syndrome. *J Clin Med.* 2017;6(11):99.
13. Domżał-Magrowska D, Kowalski MK, Szcześniak P, et al. The prevalence of celiac disease in patients with irritable bowel syndrome and its subtypes. *Prz Gastroenterol.* 2016;11(4):276-281.
14. Smalley W, Falck-Ytter C, Carrasco-Labra A, et al. AGA Clinical practice guidelines on the laboratory evaluation of functional diarrhea and diarrhea-predominant irritable bowel syndrome in adults (IBS-D). *Gastroenterology.* 2019;157(3):851-854.
15. Menees SB, Powell C, Kurlander J, et al. 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.
16. Ringström G, Abrahamsson H,

Strid H, Simrén M. Why do subjects with irritable bowel syndrome seek health care for their symptoms? *Scand J Gastroenterol*. 2007;42(10):1194-1203.

17. Chey WD, Nojkov B, Rubenstein JH, et al. The yield of colonoscopy in patients with non-constipated irritable bowel syndrome: results from a prospective, controlled US trial. *Am J Gastroenterol*. 2010;105(4):859-865.
18. Lenhart A, Ferch C, Shaw M, Chey WD. Use of dietary management in irritable bowel syndrome: results of a survey of over 1500 United States gastroenterologists. *J Neurogastroenterol Motil*. 2018;24(3):437-451.
19. 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.
20. Pandey KR, Naik SR, Vakil BV. Probiotics, prebiotics and synbiotics - a review. *J Food Sci Technol*. 2015;52(12):7577-7587.
21. Lacy BE, Pimentel M, Brenner DM, et al. ACG clinical guideline: management of irritable bowel syndrome. *Am J Gastroenterol*. 2021;116(1):17-44.
22. Chumpitazi BP, Kearns GL, Shulman RJ. The physiological effects and safety of peppermint oil and its efficacy in irritable bowel syndrome and other functional disorders. *Aliment Pharmacol Ther*. 2018;47(6):738-752.
23. Banerjee A, Sarkhel S, Sarkar R, Dhali GK. Anxiety and depression in irritable bowel syndrome. *Indian J Psychol Med*. 2017;39(6):741-745.
24. National Collaborating Centre for Nursing and Supportive Care (UK). *Irritable Bowel Syndrome in Adults: Diagnosis and Management of Irritable Bowel Syndrome in Primary Care*. London, United Kingdom: Royal College of Nursing (UK); February 2008.
25. Zhou C, Zhao E, Li Y, et al. Exercise therapy of patients with irritable bowel syndrome: a systematic review of randomized controlled trials. *Neurogastroenterol Motil*. 2019;31(2):e13461.
26. Pimentel M. Evidence-based management of irritable bowel syndrome with diarrhea. *Am J Manag Care*. 2018;24(3 suppl):S35-S46.
27. Brenner DM, Sayuk GS. Current US Food and Drug Administration-approved pharmacologic therapies for the treatment of irritable bowel syndrome with diarrhea. *Adv Ther*. 2020;37:83-96.
28. US Food and Drug Administration. Highlights of prescribing information for eluxadoline. FDA label. 2018. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/206940s006lbl.pdf.
29. Understanding the benefits and risks: the Lotronex REMS program prescriber education slide deck. 2016. https://lotronexrems.com/pdf/REMS_Prgm_Slide_Deck_FINAL_03232016.pdf.
30. Chey WD, Shah ED, DuPont HL. Mechanism of action and therapeutic benefit of rifaximin in patients with irritable bowel syndrome: a narrative review. *Therap Adv Gastroenterol*. 2020;13:1756284819897531.
31. Bajor A, Törnblom H, Rudling M, et al. Increased colonic bile acid exposure: a relevant factor for symptoms and treatment in IBS. *Gut*. 2015;64(1):84-92.
32. Slattery SA, Niaz O, Aziz Q, et al. 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.
33. Love BL. Plecanatide for treatment of chronic constipation and irritable bowel syndrome. *Am J Med*. 2019;132(5):572-575.
34. Kamuda JA, Mazzola N. Plecanatide (Trulance) for chronic idiopathic constipation and irritable bowel syndrome with constipation. *P T*. 2018;43(4):207-232.
35. Chandar AK. Diagnosis and treatment of irritable bowel syndrome with predominant constipation in the primary-care setting: focus on linaclotide. *Int J Gen Med*. 2017;10:385-393.
36. Thomas RH, Allmond K. Linaclotide (Linzess) for irritable bowel syndrome with constipation and for chronic idiopathic constipation. *P T*. 2013;38(3):154-160.
37. Cuppoletti J, Malinowska DH, Tewari KP, et al. SPI-0211 activates T84 cell chloride transport and recombinant human ClC-2 chloride currents. *Am J Physiol Cell Physiol*. 2004;287:C1173-C1183.
38. Agar JL, Schröder A, Gormsen LK, et al. Imipramine versus placebo for multiple functional somatic syndromes (STreSS-3): a double-blind, randomised study [correction *Lancet Psychiatry*. 2017;4(7):516]. *Lancet Psychiatry*. 2017;4(5):378-388.
39. Oh SJ, Takakura W, Rezaie A. Shortcomings of trials assessing antidepressants in the management of irritable bowel syndrome: a critical review. *J Clin Med*. 2020;9(9):2933.

Web resource

A. npwh.org/courses/home/details/1633