This supplement is jointly provided by Gi Health Foundation and Purdue University College of Pharmacy and is supported by educational grants from Salix Pharmaceuticals and Takeda Pharmaceuticals U.S.A, Inc. It was edited and peer reviewed by *The Journal of Family Practice.*

SUPPLEMENT TO
THE JOURNAL OF
FAMILY
PRACTICE®

VOL 70, NO 1 SUPPL[ii] | JANUARY/FEBRUARY 2021 | MDEDGE.COM/FAMILYMEDICINE

Up-to-Date Diagnosis and Management of IBS and Chronic Constipation in Primary Care

To claim credits for this activity, please visit: www.gihealthfoundation.org/EVAL-PRIMESUPPLEMENT

Up-to-Date Diagnosis and Management of IBS and Chronic Constipation in Primary Care

Baharak Moshiree, MD, MSc, FACG, AGAF; Satish Rao, MD, PhD, FRCP (LON), FACG, AGAF

doi: 10.12788/jfp.0135

CONTINUING MEDICAL EDUCATION

Baharak Moshiree, MD, MSc, FACG, AGAF
Professor of Medicine
Director of Motility
University of North Carolina, Department of Medicine
Atrium Health Gastroenterology and Hepatology
Charlotte, NC

Satish Rao, MD, PhD, FRCP (LON), FACG, AGAF
J. Harold Harrison MD Distinguished University Chair in Gastroenterology
Professor of Medicine
Augusta University Medical Center
Augusta, GA

TARGET AUDIENCE

This CME monograph is targeted at primary care physicians and allied health care providers.

GOAL STATEMENT

The goal of this monograph will focus on emerging treatment updates, reviewing current treatment guidelines, and advances in the management of irritable bowel syndrome (IBS).

EDUCATIONAL OBJECTIVES

After completing this activity, participants should be better able to:

- Recognize symptoms of IBS and chronic constipation and describe strategies for diagnosing these conditions
- Identify patients with alarm symptoms who require further diagnostic investigation
- Describe the evidence regarding the efficacy and safety of conventional and newer therapies for IBS and chronic constipation
- Understand mechanisms and specific symptoms targeted by the newer IBS therapies

ACCREDITATION STATEMENT

This activity has been planned and implemented in accordance with the accreditation requirements and policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint providership of Purdue University College of Pharmacy and the Gi Health Foundation. Purdue University College of Pharmacy, an equal access/equal opportunity institution, is accredited by the ACCME to provide continuing medical education for physicians.

CREDIT DESIGNATION

Purdue University College of Pharmacy designates this journal supplement for a maximum of 1.0 *AMA PRA Category 1 Credit*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

AAFP (AMERICAN ACADEMY OF FAMILY PHYSICIANS) ACCREDITATION

The AAFP has reviewed IBS Prime Journal Supplement and deemed it acceptable for up to 2.00 Medical Journals, Self-Study AAFP Prescribed credit. Term of Approval is from 01/01/2021 to 12/31/2021. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

PHARMACIST ACCREDITATION STATEMENT

Purdue University College of Pharmacy is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education. This is a knowledge based, continuing education activity of Purdue University, an equal access/equal opportunity institution. Universal Activity Number (UAN): 0018 – 9999-20-040-H01-P, 1.0 contact hour (0.1 CEU). Release date 1/1/21; Expiration date 12/31/21.

NURSING ACCREDITATION STATEMENT

Purdue University Continuing Nursing Education is accredited as a provider of nursing continuing professional development by the American Nurses Credentialing Center's Commission on Accreditation.

This program has been approved for 1.0 contact hour.

DISCLOSURE STATEMENT

All faculty, staff and reviewers involved in the planning, review or presentation of continuing education activities provided by Purdue University College of Pharmacy are required to disclose to the audience any relevant commercial financial affiliations related to the content of the presentation or enduring material. Full disclosure of all commercial relationships must be made in writing to the audience prior to the activity.

All additional planning committee members, staff and reviewers of The GI Health Foundation and Purdue University College of Pharmacy have no relationships to disclose.

DISCLOSURES

Satish Rao discloses that he is on advisory boards for In Control Medical, Ironwood Pharmaceuticals, Neurogut, Inc., Progenity, Quin-Tron, Takeda Pharmaceuticals, Valeant Pharmaceuticals, and Vibrant; and that he has received research grants from Progenity, Valeant Pharmaceuticals, and Vibrant.

Baharak Moshiree discloses that he is on advisory boards for Salix and Takeda; that he has received research grants from Allergan, Progenity, Salix, Takeda, and Urovant; and that he participates in speakers bureaus for QOL Medical, Salix, and Takeda. Julianne Messick, PharmD (medical writer) discloses she has no conflicts of interest.

This program is supported by educational grants from Salix Pharmaceuticals and Takeda Pharmaceuticals U.S.A., Inc.

Provided by GI Health Foundation
Accredited by PURDUE UNIVERSITY

INTRODUCTION

Abdominal pain, bloating, diarrhea, and constipation are common complaints encountered in primary care clinics, and usually suggest problems affecting the lower half of the gastrointestinal (GI) tract.[1,2] The most common diagnoses for patients with these symptoms, when chronic in nature, are irritable bowel syndrome (IBS) and chronic constipation,[3] with an estimated pooled community prevalence of 11.2%[4] and 14%,[5] respectively. Using more restrictive Rome IV diagnostic criteria, recent population-based data indicate a 4.5% prevalence of IBS and a 7.8% prevalence of functional constipation among adults across the United States, Canada, and United Kingdom.[2] IBS and chronic constipation are about twice as common in females than males,[4,5] and while IBS is more common in younger age groups, constipation tends to be higher in older populations.[4,5]

IBS and chronic constipation represent a substantial burden to patients and society in terms of daily symptoms, quality of life (QoL), work productivity, and health care costs.[6–10] Indeed, patients experience chronic, disruptive symptoms for many years prior to seeking health care and typically report lengthy and complex treatment histories.[7,9–11] Results from the IBS in America survey indicate that most patients with constipation-predominant IBS (IBS-C) experience symptoms at least 4 to 6 days per week,[11] while another survey found that more than one half of patients with diarrhea-predominant IBS (IBS-D) reported experiencing fecal urgency most of the time.[9] Abdominal pain, experienced by all subtypes of IBS, is an important symptom and a key driver of health care–seeking behavior,[7] as well as the main QoL domains of general health, social functioning, and mental health.[12]

IBS and chronic constipation are heterogeneous disorders, characterized by diverse clinical presentations and complex pathophysiologic mechanisms. IBS is considered a disorder of gut–brain interactions, with contributions from abnormalities in GI motility, visceral sensation, intestinal and colonic permeability, GI immune cell activation, and the gut microbiota.[1,13–16] Genetic polymorphisms and environmental factors, including dietary and enteric factors, also appear to play a role in some patients.[17] Indeed, acute infectious gastroenteritis remains among the strongest risk factors for IBS, leading to symptoms consistent with IBS in 10% of patients after infection (ie, postinfectious IBS).[17] Although IBS clearly results from a multifactorial process, it is uncertain whether IBS symptoms arise as a result of an abnormal stress response to infectious and/or inflammatory gut responses (ie, the brain–gut pathway), or as a result of changes in the gut microbiome leading to the release of inflammatory mediators that permanently affect the central nervous system (ie, the gut–brain axis).[15]

PATIENT CASE 1

BD is a 32-year-old woman who presents with crampy lower abdominal pain with bloating occurring on most days for more than 10 years (**TABLE 1**). She passes 3 to 4 loose stools daily and has fecal urgency. She has had a few accidents with fecal leakage, and fear of fecal leakage causes her a great deal of anxiety while at work.

Does she have IBS? In most cases, the diagnosis of IBS can be made through taking a careful history and performing a physical examination, to identify key symptoms and exclude alarming problems.[1,3,15] Abdominal pain is a cardinal feature of IBS, and its absence precludes the diagnosis of IBS.[1] According to the Rome IV diagnostic criteria (**TABLE 2**), patients with IBS have a history of disordered bowel habits (eg, diarrhea, constipation, or both), a pattern that may either improve or worsen episodes of abdominal pain. Abdominal bloating is present in most patients with IBS but is not required for diagnosis.[1]

Patients meeting the Rome IV criteria can be diagnosed with IBS provided alarm features have been appropriately excluded (**TABLES 2 AND 3**).[1] Such features include rectal bleeding, unintentional weight loss, iron-deficiency anemia, nocturnal symptoms, and a family history of colorectal cancer, celiac disease, or inflammatory bowel disease (IBD).[15] Patients with these features should be referred for further investigation and management.[18] Although patients with these features are more likely to have organic disease, most patients will ultimately have negative results and receive a subsequent diagnosis of IBS.[13]

Once symptom-based criteria are met and the diagnosis is established, patients can be subtyped based on their predominant stool pattern and bowel habit into IBS-C, IBS-D, mixed IBS (IBS-M), or IBS unclassified (IBS-U).[1]

What diagnostic tests are needed to make a diagnosis of IBS in this patient? IBS can usually be diagnosed without an exhaustive battery of diagnostic tests, although selected testing is appropriate in some patients to distinguish organic diseases from lower GI motility disorders (**FIGURE 1**). Key organic diseases in the differential diagnosis of patients with suspected IBS with diarrhea-predominant symptoms include IBD, hormonal disturbances, enteric infections, colorectal can-

TABLE 1 **Case 1: Initial case presentation**

Initial presentation
• 32-year-old woman presenting with 10+ year history of bloating and crampy pain on most days
• Passes 3-4 loose stools per day with fecal urgency
• Fecal incontinence
• No GI bleeding
• Denies weight loss
Physical exam/history
• Appears anxious
• LLQ tenderness on palpation, but no rebound or guarding
• Normal sphincter tone on digital rectal exam without stool in anal vault
Family history
• No family history of GI diseases

Abbreviations: GI, gastrointestinal; LLQ, left lower quadrant.

TABLE 2 **Rome IV diagnostic criteria for IBS**[1]

Recurrent abdominal pain, on average, ≥1 day per week in the last 3 months, associated with ≥2 of the following criteria:
1. Related to defecation
2. Associated with a change in frequency of stool
3. Associated with a change in form (appearance) of stool
Criteria fulfilled for the last 3 months, with symptom onset ≥6 months

Abbreviations: IBS, irritable bowel syndrome.

TABLE 3 **Alarm features**[15]

Age ≥50 years, no previous colon cancer screening, and presence of symptoms
Recent change in bowel habit
Evidence of overt GI bleeding (ie, melena or hematochezia)
Nocturnal pain or passage of stools
Unintentional weight loss
Family history of colorectal cancer, celiac disease, or IBD
Palpable abdominal mass or lymphadenopathy
Evidence of iron-deficiency anemia on blood testing
Positive test for fecal occult blood

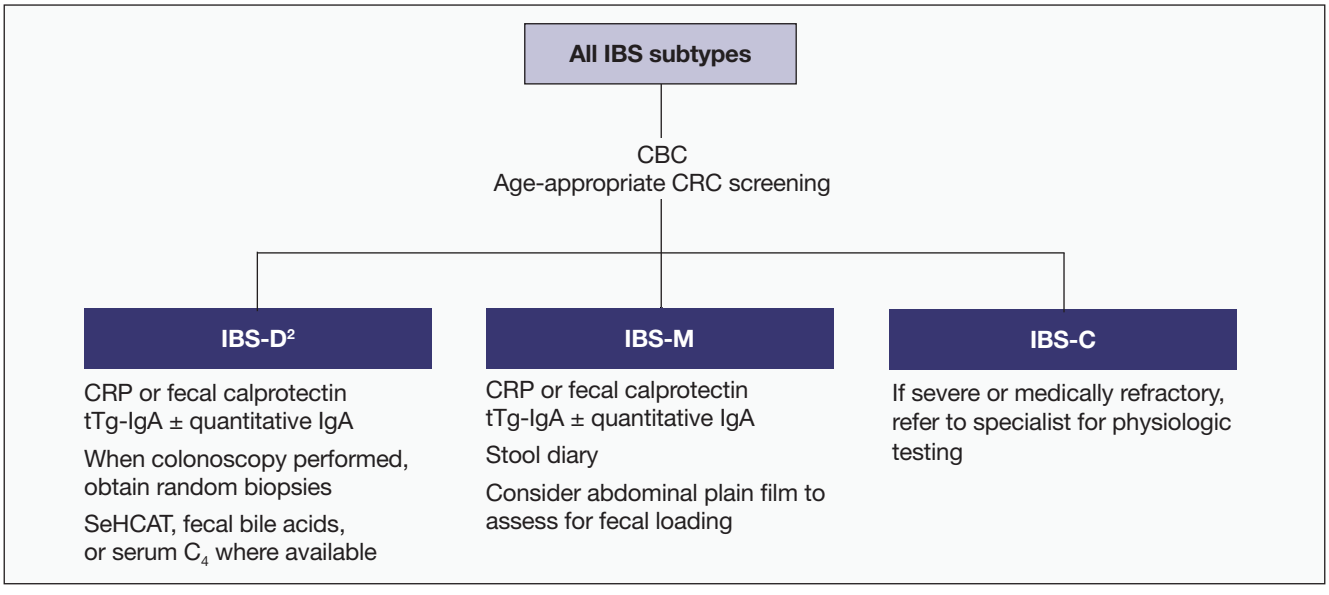
Abbreviations: GI, gastrointestinal; IBD, inflammatory bowel disease.

cer, and disorders associated with malabsorption such as celiac disease, bile acid diarrhea, or carbohydrate maldigestion.[1,13,19] To that end, a complete blood count (CBC) is typically recommended to exclude findings warranting further investigation (eg, elevated white blood cell count, anemia), while measures of systemic inflammation such as C-reactive protein (CRP) or fecal calprotectin can help discriminate between IBS and IBD with good accuracy.[1,15,20] Given its low yield in this setting,[21] routine colonoscopy is not recommended in the absence of alarm features.[1,13,15] However, because a small proportion of patients with suspected IBS-D have been found to have microscopic colitis,[21] random colon biopsies may have diagnostic value when colonoscopy is performed in this population.[13,21]

Breath tests can be useful in diagnosing various carbohydrate maldigestion syndromes as well as small intestinal bacterial overgrowth (SIBO), both of which are commonly associated with IBS-like symptoms.[22] Despite significant heterogeneity in test performance, preparations, and indications among current tests, a recent consensus of experts concluded that breath testing can be useful in diagnosing not only carbohydrate maldigestion and SIBO, but also in assessing patients with bloating and methane-associated constipation.[22] Given that up to 25% of patients with IBS-D have evidence of bile acid malabsorption regardless of whether they have had a cholecystectomy,[23] tests that identify such malabsorption may be helpful in patients with predominant diarrhea. Although the 23-seleno-25-homotaurocholic acid retention test (^{75}SeHCAT) is not currently available in the United States, blood testing for 7-C_4, a bile acid precursor, is becoming available.[15] When available, these tests may be useful in clinical practice to identify patients likely to benefit from bile acid sequestrant therapy.[13]

The value of celiac screening in patients with suspected IBS remains unclear. Current American College of Gastroenterology (ACG) guidelines recommend screening patients with IBS-like symptoms, especially in setting of iron-deficiency anemia, for celiac disease with serological testing with the tissue transglutaminase antibody (TtG) test.[24] This recommendation is supported by the results of a recent meta-analysis of 36 studies demonstrating a significantly higher prevalence of biopsy-proven celiac disease among all subtypes of IBS compared with healthy controls.[25] However, these findings were no longer significant when the analysis was restricted to North American studies or those derived from the general population, making the value of celiac disease screening in community practice less clear. Despite this conflicting evidence, clinicians are generally encouraged to have a low threshold for celiac screening in patients with IBS, particularly those with IBS-D.[1,13,15]

FIGURE 1 **Suggested diagnostic work-up for patients with suspected IBS[13]**



Abbreviations: C4, 7α-hydroxy-4-cholesten-3-one; CBC, complete blood count; CRC, colorectal cancer; CRP, C-reactive protein; IBS, irritable bowel syndrome; IBS-C, constipation-predominant IBS; IBS-D, diarrhea-predominant IBS; IBS-M, mixed IBS; IgA, immunoglobulin A; SeHCAT, selenium homocholic acid taurine; tTg, tissue transglutaminase.

PATIENT CASE 1 *(Continued))*

After confirming normal results for CBC, CRP, and celiac panel, BD's primary care physician reassures her that her symptoms are consistent with IBS-D and that no additional testing is needed at this time.

What are your first steps in managing this patient? The treatment of IBS begins by explaining the condition, reassuring the patient regarding its benign natural history, and educating the patient about possible mechanisms (gut hypersensitivity) and various treatment options.[1] Given the heterogeneity of the disorder, treatment is tailored to individual patients' predominant symptom type and severity, and no algorithm suits all patients.[1,13,15] Conventional first-line approaches are directed toward improving abdominal pain, cramping, bloating, and bowel symptoms (ie, diarrhea or constipation).

PATIENT CASE 1 *(Continued)*

When discussing potential lifestyle interventions and treatment strategies, BD notes that some foods seem to trigger her symptoms. She has tried a lactose-free diet without improvement, but has read that a gluten-free diet may be helpful.

Is a gluten-free diet beneficial for managing IBS? Despite the rising popularity of gluten restriction, its effect on IBS symptoms remains unclear. In 2 small randomized controlled trials (RCTs) in IBS patients in whom celiac disease had been excluded, gluten challenge had no statistically significant effect on IBS symptoms compared with a gluten-free diet.[26,27] Based on these data, the ACG Task Force on Management of IBS currently recommends against a gluten-free diet for overall symptom improvement in IBS.[28]

What other dietary strategies may improve symptoms in patients with IBS? The dietary strategy for IBS that has been best evaluated to date is a diet low in fermentable oligo-, di-, and monosaccharides, and polyols (FODMAPs).[28,29] Meta-analysis of 7 RCTs found a significant effect of a low FODMAP diet in improving overall symptoms of IBS,[28] with overall improvement in about half to two-thirds of patients.[29] The most likely symptoms to respond include bloating and abdominal pain, and diarrhea is more likely to improve than constipation.[29] A 2- to 4-week trial is usually sufficient to assess response, with many patients responding within the first 2 weeks of FODMAP restriction.

Despite increasing evidence supporting the benefit of a low FODMAP diet, the quality of the current evidence is low due to small numbers of patients and a high risk of bias.[28] Further, the long-term efficacy of this diet is unknown. Moreover, a low FODMAP diet is not intended to be a long-term treatment strategy, but rather a tool for identifying patients who are sensitive to FODMAPs so that some of these foods can be systematically reintro-

duced to determine which foods are triggers and individualize diets accordingly.[29] This process is best guided by a dietitian with expertise in caring for patients with GI disorders. An alternative approach may be to perform fructose, lactose, fructan, or sucrose breath tests[30,31] and/or a disaccharidase mucosal enzyme assay[32] to precisely determine ≥1 enzyme deficiency or food intolerance and provide tailored nutrition advice. However, not all these tests are widely available, some are invasive as they require upper endoscopy to obtain biopsies, and in some cases they lack accuracy.

PATIENT CASE 1 *(Continued)*

After hearing about dietary options, BD decides not to try a low FODMAP diet as she believes it will be too restrictive for her lifestyle. She reports using loperamide periodically, which typically helps her diarrhea but does not improve bloating or cramping. She has also taken an antispasmodic in the past, but this strategy has not been helpful.

What is the role of loperamide and antispasmodic agents in managing IBS-D? Loperamide, a peripheral μ-opioid receptor agonist, is often used first-line in patients with IBS-D and can be used prophylactically when a patient anticipates diarrhea.[13,15] Although loperamide is an effective antidiarrheal agent, no controlled trial evidence supports its efficacy in relieving abdominal pain, bloating, or global IBS symptoms (**TABLE 4**).[28] Similarly, despite antispasmodic agents being used for decades to treat abdominal pain associated with IBS, the evidence supporting their use is modest.[1,33] However, these agents do appear to provide some short-term benefit in IBS, but their use can be limited by dose-dependent anticholinergic adverse effects (eg, constipation, fatigue, dry mouth, dizziness, blurred vision).[13,33] Peppermint oil, which causes smooth muscle relaxation by blocking calcium channels, has been found to improve IBS symptoms in a small number of trials.[28] In particular, an enteric-coated, sustained-release formulation of peppermint oil improved symptom scores in an RCT involving 72 patients with IBS-D/M, with significant improvement observed from placebo as early as 24 hours.[34] By providing more distal delivery, this preparation appears to minimize the occurrence of heartburn that has been associated with conventional formulations.[28]

Can antidepressants help abdominal pain? Both tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs) are effective in relieving pain and overall symptoms in IBS,[33,35] likely owing to their central effects as well as their peripheral effects on pain perception, visceral hypersensitivity, and GI motility.[13,35] Although the efficacy of antidepressants according to predominant stool pattern has not been well studied, TCAs may be most appropriate in IBS-D given their ability to slow colonic motility and their mildly constipating effects.[33,35,36] The serotonin and norepinephrine reuptake inhibitors have not been studied adequately in this population.

PATIENT CASE 1 *(Continued)*

Given BD's diarrhea-predominant symptoms, a trial of a low-dose TCA would be an appropriate option, as these neuromodulators are effective for treatment of pain.[35,37]

What do you recommend to improve BD's bloating? Although status of the gut microbiome is not typically evaluated as a primary endpoint in IBS studies, increasing evidence indicates that strategies that modulate the gut microbiome may be particularly helpful in controlling bloating.[28,38] To that end, restriction of dietary FODMAPs has been found in studies of varying design to decrease bloating in a large proportion (50%-82%) of patients.[28,38] Another strategy is the use of probiotics, which are defined as attenuated bacteria or bacterial products that are beneficial to the host.[15] Based on data from 37 RCTs involving 4403 patients, the ACG Task Force on IBS determined that probiotics have low-quality evidence and therefore gave a weak recommendation for their use in treatment of IBS with possible benefit on bloating and flatulence rather than on bowel urgency or function.[28,39] However, due to the poor quality and heterogeneity of the evidence, recommendations regarding the use of particular strains or species, or the subtype of IBS most likely to respond, could not be made.[28] Also, a recent study cautioned against indiscriminate probiotic use as it may lead to colonization of probiotic organisms in the small bowel causing SIBO, D-lactic acidosis, bloating, and brain fog.[40]

Rifaximin, an oral, nonabsorbable, broad-spectrum antibiotic, has been evaluated extensively to treat IBS and was found to improve bloating in a number of studies.[14,28] Indeed, based on data from 6 RCTs involving 2441 nonconstipated IBS patients, the ACG Task Force recommends rifaximin for improvement of global IBS symptoms as well as bloating.[28] Although the precise mechanism for its benefit in IBS remains unclear, rifaximin appears to have beneficial effects on GI symptoms of diarrhea, pain and bloating, mucosal inflammation, and stabilization of the gut microbiota.[14] Further, preclinical evidence suggests that the effects of rifaximin in IBS may involve mechanisms beyond the gut microbiota,

TABLE 4 **Pharmacologic treatment of IBS-D**[1,13,15,28]

Agent	ACG systematic review of evidence				Dose	Treatment benefits
	Number of RCTs	N	RR of remaining symptomatic vs placebo (95% CI)	Strength of evidence		
Antispasmodics						
Various	26	2811	0.65 (0.56-0.76)	Very low	Dicyclomine 10-20 mg QD-QID	Some agents improve global symptoms and pain
Peppermint oil	7	634	0.54 (0.39-0.76)	Low	EC capsules 250-750 mg BID-TID	Improves global symptoms and cramping
Antidepressants						
TCAs	12	787	0.65 (0.55-0.77)	High	Desipramine 25-200 mg QHS Amitriptyline 10-50 mg QHS	Improves global symptoms and pain
5-HT_3 antagonists						
Alosetron	8	4897	0.79 (0.69-0.90)	Low	0.5-1 mg QD	Improves global, abdominal, and diarrhea symptoms in women with severe IBS-D
Opioid receptor modulators						
Loperamide	2	42	0.44 (0.14-1.42)	Very low	2-4 mg prn, up to 16 mg/d	Beneficial for diarrhea but not global symptoms or pain
Eluxadoline	3	3235	0.91 (0.85-0.97)	Moderate	75-100 mg BID	Improves global symptoms
Antibiotics						
Rifaximin	6	2441	0.86 (0.81-0.91)	Moderate	550 mg TID for 14 days	Improves global symptoms, pain, and bloating
Probiotics						
Various	37	4403	0.81 (0.74 to 0.88)	Low	Various	Possible benefits for global symptoms, bloating, and gas, but unable to recommend specific probiotic strains or formulations

Abbreviations: ACG, American College of Gastroenterology; BID, twice daily; EC, enteric-coated; HT3, hydroxytryptamine subtype 3; IBS-D, diarrhea-predominant irritable bowel syndrome; prn, as needed; QD, once daily; QHS, every night at bedtime; QID, 4 times daily; RCT, randomized controlled trial; RR, relative risk; TCA, tricyclic antidepressant; TID, 3 times daily.

including the modulation of proinflammatory cytokines and intestinal permeability.[14,41]

Rifaximin is approved in a 14-day regimen for the treatment of IBS-D and up to 2 re-treatments in patients who experience recurrence.[42] Rifaximin is well tolerated, with a safety profile similar to that of placebo.[43] The very limited risk for *Clostridium difficile* infection and/or the emergence of microbial resistance has been reassuring.[28,43,44]

Are there other therapies available for IBS-D? Alosetron is a selective serotonin 5-HT_3 receptor antagonist that has been shown to relieve global IBS symptoms and abdominal pain, in a number of large RCTs.[28] More recently, a network meta-analysis of 18 RCTs involving various therapies (alosetron, ramosetron, rifaximin, eluxadoline) ranked alosetron first in efficacy for achieving the composite endpoint of improvement in both abdominal pain and stool consistency, effect on global symptoms, and effect on stool consistency in patients with IBS-D/-M.[45] However, the use of alosetron has been limited by the small risk of ischemic colitis (1.03 cases per 1000 patient-years) and serious complications of constipation (0.25 cases per 1000 patient-years),[46] leading to the restriction of its use to women with severe IBS-D who have not responded to conventional therapies.[47] Although marketed under a Risk Evaluation and Mitigation Strategy (REMS) program, requirements for the program have been updated to make it less onerous for prescribers than when the REMS was first initiated.[37]

TABLE 5 **Case 2: Initial case presentation**

Initial presentation	
• 53-year-old man presents with of occasional constipation for years, but increasing abdominal pain and straining to have a BM most days over the past 3 years • Has 2-3 BMs per week; described as either rabbit pellets or huge, hard stools, but denies any rectal bleeding • Pain gets better after defecation • Denies weight loss • Foul-smelling, excess flatulence	
History	
Family history	No family history of GI diseases
Medical history	Seasonal allergies, GERD, diverticulosis per prior colonoscopy at age 50, DJD
Medications	• Omeprazole 20 mg/day • ASA 325 mg, multivitamin daily • Ibuprofen 2-3 times weekly
Physical exam/history	
Rectal exam	Normal rectal tone, no perianal lesions, appropriate pelvic floor descent, no masses, normal prostate size without nodularity

Abbreviations ASA, aspirin; BM, bowel movement; DJD, degenerative joint disease; GERD, gastroesophageal reflux disease; GI, gastrointestinal.

Eluxadoline is an oral, locally acting, mixed μ- and k-opioid agonist/d-opioid receptor antagonist approved for use in adults with IBS-D.[48–50] Unlike pure μ-opioid receptor agonists, this agent reduces visceral hypersensitivity without completely disrupting intestinal motility, theoretically decreasing the potential for medication-related constipation.[50,51] Meta-analysis of data from 3 large RCTs demonstrated significant benefits of eluxadoline on stool consistency and overall symptom improvement in patients with IBS-D, but failed to demonstrate a clear effect on abdominal pain.[28] However, subsequent analysis of the pivotal trials[52] and a phase 4 study[50] found eluxadoline to be effective in improving abdominal and stool consistency in patients with IBS-D who reported inadequate symptom response to loperamide. Eluxadoline has been relatively well tolerated in clinical trials, with the most common adverse effects being constipation, nausea, and vomiting.[28,48,50] However, due to the risk of pancreatitis, this agent is contraindicated in patients without a gallbladder and those with known or suspected biliary duct obstruction or sphincter of Oddi disease/dysfunction, alcohol use, history of pancreatitis, severe hepatic impairment, and severe constipation or its sequelae.[48]

PATIENT CASE 1 *(Continued)*

BD is treated with rifaximin 3 times a day for 14 days and has resolution of her crampy pain, bloating, and diarrhea. These symptoms return after 10 weeks, and she requests a re-treatment although her symptoms now are not as severe as before. Six weeks later, the patient returns for a follow-up clinic visit and reports 60% improvement in abdominal pain, bloating, and loose stools.

PATIENT CASE 2

JL is a 53-year-old man who presents with occasional constipation for several years, but increasing abdominal pain and straining to pass a bowel movement most days over the past 3 years (**TABLE 5**). He has 2 to 3 bowel movements per week, described as either rabbit pellets or huge, hard stools. The pain usually improves after defecation. His spouse complains about his foul-smelling flatulence.

How should JL be evaluated? Key steps in evaluating this patient include a careful clinical history including digital rectal exam, and physical examination combined with selected tests to exclude organic disease and evaluate constipation pathophysiology as necessary.[1,3] Given the liberal use of the term constipation, it is important to characterize his symptoms with respect to frequency and types of bowel movements, associated features, and degree of straining during defecation and use of digital maneuvers to assist defecation.[1,53] Physical exam should include abdominal examination for distention, hard stool in a palpable rectum, or a mass.[1] It is essential to perform a digital rectal exam,[54] which can help identify a fecal impaction, anal stricture, rectal mass, and/or pelvic floor dyssynergia.[1,15,53] Patients with paradoxical anal contraction on straining should be referred for physiologic testing.[13,15,18] In the absence of secondary causes for constipation, primary constipation comprises 3 overlapping subtypes: IBS-C, slow-transit constipation, and evacuation disorders such as dyssynergic defecation.[55] Whereas delayed stool transit in slow-transit constipation is attributed to underlying myopathy or neuropathy, impaired coordination of the abdominal and anorectal muscles is believed to be responsible for dyssynergic defecation.[55]

The need for laboratory testing in this patient is minimal, as he denies the presence of key alarm symptoms

TABLE 6 **Common causes of secondary constipation**[53]

Medications	
Anticholinergics	Diphenhydramine, oxybutynin
Antidepressants	TCAs
Antihistamines	Cetirizine, fexofenadine, loratadine
Calcium channel blockers	Amlodipine, diltiazem, verapamil
Diuretics	Furosemide
Iron supplements	Ferrous fumarate, ferrous sulfate
NSAIDs	Aspirin, ibuprofen, naproxen
Opioids	Hydrocodone, morphine, oxycodone
5-HT_3 antagonists	Ondansetron

Metabolic disorders
• Diabetes mellitus
• Hypercalcemia, hypokalemia, hypomagnesemia
• Hyperparathyroidism
• Hypothyroidism
• Neurologic disorders (amyloidosis, multiple sclerosis, Parkinson's disease, spinal cord injury)

Mechanical obstruction
• Anal fissures
• Colon cancer
• Strictures

Miscellaneous conditions
• Diet
• Eating disorders
• Depression
• Immobility
• Paraneoplastic syndrome

Abbreviations: HT_3, hydroxytryptamine subtype 3; NSAIDs, nonsteroidal anti-inflammatory drugs; TCA, tricyclic antidepressant.

(eg, unintentional weight loss, rectal bleeding) and has undergone recent screening colonoscopy per national recommendations. In patients with symptoms of hypothyroidism or hypercalcemia, a serum thyroid-stimulating hormone and serum calcium may be indicated.[1] Although IBS-C and chronic constipation are among the most common disorders associated with symptoms of chronic constipation, the various secondary causes of constipation should also be excluded (**TABLE 6**).[53,56]

Does he have IBS-C or chronic constipation? Does it matter? Once alarm features and secondary etiologies for constipation have been ruled out, the Rome IV criteria can be useful to diagnose JL. Chronic idiopathic constipation, or functional constipation, and IBS-C are recognized as 2 distinct conditions, with the predominance of abdominal pain being the discriminating factor for IBS-C (**TABLES 2 AND 7**).[1] Given JL's predominant complaint of abdominal pain that improves with defecation, he fulfills the Rome IV criteria for IBS-C. However, considerable symptom overlap and disease burden occurs between these 2 conditions, and many patients tend to migrate between these diagnoses over time, making it difficult to distinguish between the disorders.[1,3] Further, these conditions may exist along a spectrum of disease, with the presence of abdominal symptoms indicating disease severity rather than defining 2 separate conditions.[7] Accordingly, IBS-C and constipation are often treated similarly,[57] although the current evidence for different therapies is not always consistent between the disorders (**TABLE 8**).

PATIENT CASE 2 *(Continued)*

JL is diagnosed with IBS-C and educated regarding increasing his fluid intake, maintaining a fiber-rich diet, and the benefits of exercise. He reports that he has tried a bran fiber supplement he obtained from his local health food store, but it worsened his bloating. He has also tried polyethylene glycol (PEG), which helped loosen his stools but has not improved the abdominal pain.

Is fiber effective in managing IBS-C/chronic constipation? Poorly fermentable, soluble fiber (eg, psyllium) is a recommended, evidence-based treatment for both IBS-C and chronic constipation, increasing stool frequency and improving symptoms in both conditions (**TABLE 8**).[3,28] In contrast, insoluble fiber (eg, bran) has no significant effect on IBS symptoms and inconsistent effects in chronic constipation, and on the contrary, may increase pain and bloating.[3,28] Although an appropriate first-line treatment, fiber supplementation should be introduced gradually, starting with low doses and titrating slowly as tolerated to minimize unwanted GI effects (bloating, flatulence, and abdominal discomfort).[28,53,58,59] Patients should also be educated that unlike stimulant laxatives, response to fiber may take several weeks.[59]

TABLE 7 **Rome IV diagnostic criteria for functional constipation**[1]

Must include ≥2 of the following:

- Straining
- Lumpy or hard stools (BSFS 1-2)
- Sensation of incomplete evacuation
- Sensation of anorectal obstruction/blockage
- Manual maneuvers to facilitate >25% defecations
- <3 SBMs per week
- Loose stools are rarely present without the use of laxatives
- Insufficient criteria for IBS

Criteria should be fulfilled for the last 3 months with symptom onset ≥6 months before diagnosis.

Abbreviations: BSFS, Bristol Stool Form Scale; IBS, irritable bowel syndrome; SBM, spontaneous bowel movement.

What is the role of laxatives in treating IBS-C/chronic constipation? Stimulant laxatives (senna, bisacodyl, castor oil, cascara, and aloe) help produce bowel movements by decreasing water absorption and stimulating intestinal motility, either directly or indirectly through release of prostaglandins.[3,53] These agents are often used on a rescue basis, such as in patients who have not defecated in several days, or more regularly if required.[59,60] Based on data from 2 RCTs, the ACG Task Force considers sodium picosulfate and bisacodyl to be effective for chronic constipation,[3] although their use can be limited by poor tolerability, particularly with regard to diarrhea and abdominal cramping. There is insufficient evidence to recommend the use of other stimulant laxatives for chronic constipation, and similarly, there are no RCTs of stimulant laxatives in IBS-C.[3,13]

PEG is an osmotic laxative that extracts fluid into the intestinal lumen to soften stools and accelerate colon transit.[59] The short- and long-term efficacy of PEG has been well established in patients with chronic constipaiton,[3] with efficacy and safety established up to 6 months in an RCT[61] and 24 months in a retrospective trial.[62] Its efficacy in IBS-C, however, is less clear. Data from 2 small RCTs found that PEG improved stool frequency in patients with IBS-C, but not pain or other IBS-related symptoms.[28,63,64] Based on these data, the ACG recommends against the use of PEG for overall symptom improvement in patients with IBS.[28]

Is JL a candidate for antidepressant therapy? As mentioned previously, both TCAs and SSRIs are effective in relieving pain and overall symptoms in IBS.[28] Given their prokinetic and anxiolytic effects, an SSRI is an appropriate option for JL,[13,36] who is experiencing significant anxiety concurrent with his constipation-related symptoms. When used for IBS-C, these agents are usually initiated at low doses, and 4 to 8 weeks may be needed for maximal response.[13,36,65]

PATIENT CASE 2 *(Continued)*

JL is started on a trial of psyllium, starting with 1 teaspoon once daily and increasing weekly as tolerated, and citalopram 20 mg daily. After 6 weeks, he returns for follow-up. He reports considerable improvement in his anxiety and modest improvement in his bowel frequency, but neither the abdominal pain nor the bloating have improved.

Should a prosecretory agent be prescribed? The use of a prosecretory agent (lubiprostone, linaclotide, plecanatide, and tenapanor) is generally considered appropriate in patients such as JL who have not responded to an adequate trial of first-line approaches for IBS-C/chronic constipation, including lifestyle and dietary modification, soluble fiber, and/or PEG.[15,58] These therapies, also called secretagogues, act on intestinal enterocytes to stimulate net efflux of ions and water into the intestinal lumen, accelerate intestinal transit, and facilitate ease of defecation.[15,59] These agents significantly improve bowel and abdominal symptoms in IBS-C,[28,66] and are approved for this use.[67–70] The efficacy of lubiprostone, linaclotide, and plecanatide has also been well established in chronic constipation.[3]

Lubiprostone is a prostaglandin E_1 derivative that acts on type 2 chloride channels (ClC2) of small intestinal enterocytes to increase secretion of chloride and fluid into the intestinal lumen.[28,59,71] This agent is approved at dosages of 8 µg twice daily for IBS-C and 24 µg twice daily for chronic constipation. The most common adverse effect with lubiprostone in pivotal trials of IBS-C and chronic constipation is dose-related nausea, occurring in 8% and 29% of patients receiving 8 µg and 24 µg twice daily, respectively (compared with 4% and 3% of patients receiving placebo).[68,72] Lubiprostone should be taken with food and water to minimize nausea, and treatment can be initiated at lower doses and titrated upward as needed.[13,68]

Linaclotide and plecanatide are guanylate cyclase (GC)-C agonists that mimic the endogenous peptides guanylin and uroguanylin in activating chloride ion secretion through the cystic fibrosis transmembrane regulator (CFTR), increasing fluid secretion into the GI tract and accelerating intestinal transit.[73,74] Additionally, because

TABLE 8 **ACG Task Force on IBS/CIC* Systematic Reviews on Pharmacologic Treatment of IBS-C and chronic constipation[a]**

	IBS-C[28]				Chronic constipation[3]			
Agent	**Number of RCTs**	**N**	**RR of remaining symptomatic vs placebo (95% CI)**	**Strength of evidence**	**Number of RCTs**	**N**	**RR of remaining symptomatic vs placebo (95% CI)**	**Strength of evidence**
Fiber								
Insoluble fiber (eg, bran)	6	441	0.90 (0.79-1.03)	Moderate	3[b]	293	0.25 (0.16-0.37)	Low
Soluble fiber (eg, psyllium)	7	499	0.83 (0.73-0.94)	Moderate				
Laxatives								
Stimulants					2	735	3 (2-3.5)	Moderate
PEG	2	181	—[c]	Low	4	573	0.52 (0.41-0.65)	High
Antidepressants								
SSRIs	7	356	0.68 (0.51-0.91)	Low				
Prosecretory agents								
Lubiprostone	3	1366	0.91 (0.87-0.95)	Moderate	4	651	0.67 (0.58-0.77)	High
Linaclotide	4	2867	0.81 (0.77-0.85)	High	3	1582	0.84 (0.80-0.87)	High
Plecanatide	3	2612	0.88 (0.84-0.92)	Moderate				
Prokinetic agents								
Prucalopride					8	3140	0.81 (0.75-0.86)	Moderate

*Chronic idiopathic constipation (CIC) is another term for chronic constipation.

[a]Tenapanor and tegaserod were not included in the ACG systematic reviews on IBS-C and chronic idiopathic constipation. Plecanatide was not included in the ACG systematic review on chronic constipation.

[b]2 trials used psyllium and 1 trial used inulin/maltodextrose combination.

[c]No dichotomous data reported.

Abbreviations: CI, confidence interval; IBS, irritable bowel syndrome; IBS-C, constipation-predominant IBS; PEG, polyethylene glycol; RCT, randomized controlled trial; RR, relative risk; SSRI, selective serotonin reuptake inhibitor.

GC-C pathways are involved in modulating pain fiber activity,[75–77] these agents have effects on the abdominal pain and sensory symptoms of patients with IBS-C.[76,78,79] In clinical trials with linaclotide, however, improvement in stool frequency tends to occur earlier (ie, within a week of treatment initiation) than improvement in abdominal pain and bloating, which make take up to 8 to 12 weeks.[13,73] A recent study showed that linaclotide improves abdominal pain in IBS-C by improving rectal hypersensitivity and attenuating the signals from the rectum to the brain.[80]

Both linaclotide and plecanatide are approved at once-daily doses for use in IBS-C and chronic constipation (**TABLE 9**).[69,70,73,74] The most common adverse effect of these therapies is diarrhea, which is typically mild and leads to few treatment discontinuations.[69,70] Diarrhea associated with linaclotide can be managed by administering the agent 30 to 60 minutes before breakfast,[13,78] and/or by initiating therapy with a low dose (72 µg/d) and titrating upwards as needed.

Tenapanor is a minimally absorbed, small-molecule

TABLE 9 **Practical considerations for pharmacologic treatment of IBS-C and chronic constipation**[13,15,59,67,74,81,82]

Treatment	Dose		Treatment benefits	Most common adverse effects
	IBS-C	Chronic constipation		
Fiber				
Psyllium	Up to 30 g in 1-3 doses per day	Up to 30 g in 1-3 doses per day	Improves stool consistency and frequency, and overall symptom relief	Bloating, gas, cramping
Laxatives				
Bisacodyl		5-10 mg QD	Effective in chronic constipation; no RCT data in IBS-C	Abdominal cramping, diarrhea, colonic staining; Caution in those with laxative abuse
Senna		6.2-34.4 mg		
PEG	17-34 g QD	17-34 g QD	Improves constipation but not global symptoms or pain in IBS-C	Bloating, cramping, nausea, diarrhea, increased gas
Antidepressants				
SSRIs	Paroxetine 10-40 mg QD Sertraline 25-100 mg QD Citalopram 10-40 mg QD		Improves global symptoms and pain; appropriate for patients with prominent anxiety	Nausea, diarrhea, sexual dysfunction
Prosecretory agents				
Linaclotide	290 µg QD	72-145 µg QD	Improves global, abdominal, and constipation symptoms	Diarrhea
Lubiprostone	8 µg BID	24 µg BID	Improves global, abdominal, and constipation symptoms	Nausea, diarrhea
Plecanatide	6 mg QD	3 or 6 mg QD	Improves global, abdominal, and constipation symptoms	Diarrhea
Tenapanor	50 mg BID			Diarrhea, headache, nausea
Prokinetic agents				
Prucalopride		2 mg QD[a]	Improves constipation symptoms, stool frequency and stool consistency	Nausea, diarrhea, headache, abdominal pain
Tegaserod	6 mg BID[b]		Improves constipation symptoms	Diarrhea, headache, nausea, possible increase in CV events (unproven)

[a]1 mg QD recommended in older patients and those with renal or hepatic impairment.

[b]Approved for women with IBS-C age <65 years.

Abbreviations: BID, twice daily; CV, cardiovascular; QD, once daily; RCT, randomized controlled trial; RR, relative risk; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

inhibitor of the GI sodium/hydrogen exchanger isoform 3 (NH3) that increases intestinal fluid volume and transit by inhibiting the absorption of dietary sodium and phosphate.[66,81,82] Approved for IBS-C in 2019,[67] this agent has demonstrated efficacy in improving both abdominal and global IBS symptoms in 2 large phase 3 RCT.[66,67] Diarrhea is the most common adverse effect associated with tenapanor, leading to discontinuation in 6.5% of patients receiving this therapy compared with 0.7% of placebo-treated patients.[67]

What other treatment options are available for IBS-C/chronic constipation? Although early experience with prokinetic agents, or 5-HT_4 agonists, was mired by reports of adverse cardiovascular events, newer 5-HT_4 agonists with greater receptor selectivity are now available (prucalopride)[83] or are under investigation (naronapride)[82]

for use in functional GI disorders. Unlike the nonselective 5-HT_4 agonist cisapride, which was withdrawn from the market due to its proarrhythmic effects, these newer agents stimulate gastric motility without off-target interactions due to their high selectivity for 5-HT_4 receptors.[82,84]

Prucalopride is a highly selective 5-HT_4 agonist that stimulates intestinal motility by interacting with 5-HT_4 receptors throughout the GI tract.[82,84,85] Marketed in other countries for over a decade,[86] this agent was approved by the US Food and Drug Administration (FDA) in 2018 for the treatment of chronic constipation in adults.[83] The efficacy of prucalopride in improving frequency of bowel movement, bowel symptoms, and health-related QoL in chronic constipation is supported by a large body of evidence.[3,84] Prucalopride has demonstrated efficacy in multiple populations, including men and women,[84,87,88] patients dissatisfied with previous laxatives,[87,89] and elderly patients.[90] Further, the efficacy of prucalopride has demonstrated for up to 18 months.[91] Therapy with prucalopride has been well tolerated, with headache, abdominal pain, nausea, and diarrhea being the most commonly reported adverse effects.[83,92] These effects appear to be transient, typically subsiding within the first week of treatment.[58] Importantly, no concerns for cardiovascular adverse events have emerged.[84,92] Given its action on serotonin, patients on this drug should be monitored for depression.

Tegaserod is a partial 5-HT_4 agonist that was voluntarily withdrawn from the US market in 2007 following reports of rare, but apparently associated, ischemic cardiovascular events.[85,93] In April 2019, the FDA reviewed extensive supplementary data from 29 RCTs and approved the use of tegaserod for IBS-C in women younger than 65 years of age without a history of cardiovascular ischemic disease and who have no more than one risk factor for cardiovascular disease.[59] In 3 RCTs involving 2470 women, tegaserod significantly improved the frequency of bowel movements while also reducing abdominal pain/discomfort and bloating.[94] The most common adverse effects associated with tegaserod include headache, nausea, and diarrhea, with diarrhea typically resolving with continued therapy and leading to discontinuation in only 1.6% of patients.[94]

PATIENT CASE 2 *(Continued)*

Linaclotide is initiated at a dose of 145 µg/day, taken 30 minutes before breakfast. During a follow-up telephone call 3 weeks later, he reported having a soft bowel movement every day and that the abdominal pain and bloating were improved.

CONCLUSIONS

IBS and chronic constipation are extremely common disorders associated with considerable burden due to chronic, daily symptoms and high levels of dissatisfaction with therapy. Fortunately, however, advances in understanding of the pathogenesis of these disorders have paved the way for new treatments, and the evidence base has grown considerably over time. With growing awareness of the potential contribution of certain foods to symptoms, dietary intervention, particularly the low-FODMAP diet, has gained importance as a therapeutic strategy for many IBS-D patients. Among the common medical therapies for IBS-D, the best clinical trial evidence supports the use of alosetron, TCAs, enteric-coated peppermint oil, rifaximin, and eluxadoline. Although the predominance of abdominal pain differentiates IBS-C from chronic constipation, significant overlap exists and treatment options are largely similar, with some differences. First-line treatment of IBS-C/chronic constipation typically consists of diet and lifestyle modifications, along with nonprescription laxatives (soluble fiber, PEG). High-quality evidence supports the efficacy of prosecretory (lubiprostone, linaclotide, plecanatide, tenapanor) and prokinetic agents (prucalopride, tegaserod) for patients not responding to first-line measures. ●

REFERENCES

1. Mearin F, Lacy BE, Chang L, et al. Bowel disorders. *Gastroenterology.* 2016;150:1393-1407.
2. Palsson OS, Whitehead W, Törnblom H, et al. Prevalence of Rome IV functional bowel disorders among adults in the United States, Canada, and the United Kingdom. *Gastroenterology.* 2020;158(5):1262-1273.e3.
3. Ford AC, Moayyedi P, Lacy BE, et al. 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.
4. Lovell RM, Ford AC. Global prevalence of and risk factors for irritable bowel syndrome: a meta-analysis. *Clin Gastroenterol Hepatol.* 2012;10(7):712-721.e4.
5. Suares NC, Ford AC. Prevalence of, and risk factors for, chronic idiopathic constipation in the community: systematic review and meta-analysis. *Am J Gastroenterol.* 2011;106(9):1582-1591.
6. 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.
7. Heidelbaugh JJ, Stelwagon M, Miller SA, et al. The spectrum of constipation-predominant irritable bowel syndrome and chronic idiopathic constipation: US survey assessing symptoms, care seeking, and disease burden. *Am J Gastroenterol.* 2015;110(4):580-587.
8. Nellesen D, Yee K, Chawla A, et al. A systematic review of the economic and humanistic burden of illness in irritable bowel syndrome and chronic constipation. *J Manag Care Pharm.* 2013;19(9):755-764.
9. 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.
10. Taylor DCA, Abel JL, Martin C, et al. Comprehensive assessment of patients with irritable bowel syndrome with constipation and chronic idiopathic constipation using deterministically linked administrative claims and patient-reported data: the Chronic Constipation and IBS-C Treatment and Out-

comes Real-World Research Platform (CONTOR). *J Med Econ.* 2020;23(10):1072-1083.

11. American Gastroenterological Association. IBS in America: survey summary findings. https://www.multivu.com/players/English/7634451-aga-ibs-in-america-survey/docs/survey-findings-pdf-635473172.pdf. Published December 2015. Accessed November 2, 2020.
12. Taylor DCA, Abel JL, Doshi JA, et al. The impact of stool consistency on bowel movement satisfaction in patients with IBS-C or CIC treated with linaclotide or other medications: real-world evidence from the CONTOR Study. *J Clin Gastroenterol.* 2019;53(10):737-743.
13. Chey WD, Kurlander J, Eswaran S. Irritable bowel syndrome: a clinical review. *JAMA.* 2015;313(9):949-958.
14. Chey WD, Shah ED, DuPont HL. Mechanism of action and therapeutic benefit of rifaximin in patients with irritable bowel syndrome: a narrative review. *Ther Adv Gastroenterol.* 2020;13:1756284819897531.
15. Ford AC, Lacy BE, Talley NJ. Irritable bowel syndrome. *N Engl J Med.* 2017;376(26):2566-2578.
16. Pimentel M, Lembo A. Microbiome and its role in irritable bowel syndrome. *Dig Dis Sci.* 2020;65(3):829-839.
17. 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.e7.
18. 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.
19. American College of Gastroenterology Task Force on IBS; Brandt LJ, Chey WD, et al. An evidence-based position statement on the management of irritable bowel syndrome. *Am J Gastroenterol.* 2009;104(suppl 1):S1-S35.
20. Banerjee A, Srinivas M, Eyre R, et al. Faecal calprotectin for differentiating between irritable bowel syndrome and inflammatory bowel disease: a useful screen in daily gastroenterology practice. *Frontline Gastroenterol.* 2015;6(1):20-26.
21. 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.
22. Rezaie A, Buresi M, Lembo A, et al. Hydrogen and methane-based breath testing in gastrointestinal disorders: the North American Consensus. *Am J Gastroenterol.* 2017;112(5):775-784.
23. 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.
24. Rubio-Tapia A, Hill ID, Kelly CP, et al; American COG. ACG clinical guidelines: diagnosis and management of celiac disease. *Am J Gastroenterol.* 2013;108(5):656-676.
25. Irvine AJ, Chey WD, Ford AC. Screening for celiac disease in irritable bowel syndrome: an updated systematic review and meta-analysis. *Am J Gastroenterol.* 2017;112(1):65-76.
26. Biesiekierski JR, Newnham ED, Irving PM, et al. Gluten causes gastrointestinal symptoms in subjects without celiac disease: a double-blind randomized placebo-controlled trial. *Am J Gastroenterol.* 2011;106(3):508-514.
27. Shahbazkhani B, Sadeghi A, Malekzadeh R, et al. Non-celiac gluten sensitivity has narrowed the spectrum of irritable bowel syndrome: a double-blind randomized placebo-controlled trial. *Nutrients.* 2015;7(6):4542-4554.
28. Ford AC, Moayyedi P, Chey WD, et al. American College of Gastroenterology monograph on management of irritable bowel syndrome. *Am J Gastroenterol.* 2018;113:1-18.
29. Chey WD. Food: the main course to wellness and illness in patients with irritable bowel syndrome. *Am J Gastroenterol.* 2016;111(3):366-371.
30. Amieva-Balmori M, Coss-Adame E, Rao NS, et al. Diagnostic utility of carbohydrate breath tests for SIBO, fructose, and lactose intolerance. *Dig Dis Sci.* 2020;65(5):1405-1413.
31. Rao SS, Yu S, Fedewa A. Systematic review: dietary fibre and FODMAP-restricted diet in the management of constipation and irritable bowel syndrome. *Aliment Pharmacol Ther.* 2015;41(12):1256-1270.
32. Viswanathan L, Rao SSC, Kennedy K, et al. Prevalence of disaccharidase deficiency in adults with unexplained gastrointestinal symptoms. *J Neurogastroenterol Motil.* 2020;26(3):384-390.
33. Ford AC, Harris LA, Lacy BE, et al. 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.
34. Cash BD, Epstein MS, Shah SM. A novel delivery system of peppermint oil is an effective therapy for irritable bowel syndrome. *Dig Dis Sci.* 2016;61(2):560-571.
35. Ford AC, Lacy BE, Harris LA, et al. Effect of antidepressants and psychological therapies in irritable bowel syndrome: an updated systematic review and meta-analysis. *Am J Gastroenterol.* 2019;114(1):21-39.
36. Dekel R, Drossman DA, Sperber AD. The use of psychotropic drugs in irritable bowel syndrome. *Expert Opin Invest Drugs.* 2013;22(3):329-339.
37. 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.
38. Foley A, Burgell R, Barrett JS, Gibson PR. Management strategies for bloating and abdominal distension. *Gastroenterol Hepatol (N Y).* 2014;10(9):561-571.
39. Camilleri M. Management options for irritable bowel syndrome. *Mayo Clin Proc.* 2018;93(12):1858-1872.
40. Rao SSC, Yu S, Tetangco EP, et al. Probiotics can cause D-lactic acidosis and brain fogginess: reply to Quigley et al. *Clin Transl Gastroenterol.* 2018;9(11):207.
41. Pimentel M. Review article: potential mechanisms of action of rifaximin in the management of irritable bowel syndrome with diarrhoea. *Aliment Pharmacol Ther.* 2016;43:37-49.
42. Xifaxan [package insert]. Bridgewater, NJ: Salix Pharmaceuticals, a division of Bausch Health US, LLC; 2019.
43. Schoenfeld P, Pimentel M, Chang L, et al. Safety and tolerability of rifaximin for the treatment of irritable bowel syndrome without constipation: a pooled analysis of randomised, double-blind, placebo-controlled trials. *Aliment Pharmacol Ther.* 2014;39(10):1161-1168.
44. Appleby RN, Walters JR. The role of bile acids in functional GI disorders. *Neurogastroenterol Motil.* 2014;26(8):1057-1069.
45. Black CJ, Burr NE, Camilleri M, et al. Efficacy of pharmacological therapies in patients with IBS with diarrhoea or mixed stool pattern: systematic review and network meta-analysis. *Gut.* 2020;69(1):74-82.
46. Tong K, Nicandro JP, Shringarpure R, et al. A 9-year evaluation of temporal trends in alosetron postmarketing safety under the risk management program. *Ther Adv Gastroenterol.* 2013;6(5):344-357.
47. Lotronex [package insert]. Roswell, GA: Sebila Pharmaceuticals Inc; 2016.
48. Viberzi [package insert]. Madison, NJ: Allergan USA, Inc; 2020.
49. Liu R, Staller K. Update on eluxadoline for the treatment of irritable bowel syndrome with diarrhea: patient selection and perspectives. *Drug Des Devel Ther.* 2020;14:1391-1400.
50. Brenner DM, Sayuk GS, Gutman CR, et al. Efficacy and safety of eluxadoline in patients with irritable bowel syndrome with diarrhea who report inadequate symptom control with loperamide: RELIEF phase 4 study. *Am J Gastroenterol.* 2019;114(9):1502-1511.
51. Lembo AJ, Lacy BE, Zuckerman MJ, et al. Eluxadoline for irritable bowel syndrome with diarrhea. *N Engl J Med.* 2016;374(3):242-253.
52. Lacy BE, Chey WD, Cash BD, et al. Eluxadoline efficacy in IBS-D patients who report prior loperamide use. *Am J Gastroenterol.* 2017;112(6):924-932.
53. Lacy BE. Update on the management of chronic idiopathic constipation. *Am J Manag Care.* 2019;25(4 suppl):S55-S62.
54. Rao SSC. Rectal exam: yes, it can and should be done in a busy practice. *Am J Gastroenterol.* 2018;113(5):635-638.
55. Rao SS, Patcharatrakul T. Diagnosis and treatment of dyssynergic defecation. *J Neurogastroenterol Motil.* 2016;22(3):423-435.
56. Rao SSC, Rattanakovit K, Patcharatrakul T. Diagnosis and management of chronic constipation in adults. *Nat Rev Gastroenterol Hepatol.* 2016;13(5):295-305.
57. Eswaran S, Guentner A, Chey WD. Emerging pharmacologic therapies for constipation-predominant irritable bowel syndrome and chronic constipation. *J Neurogastroenterol Motil.* 2014;20(2):141-151.
58. Aziz I, Whitehead WE, Palsson OS, et al. An approach to the diagnosis and management of Rome IV functional disorders of chronic constipation. *Expert Rev Gastroenterol Hepatol.* 2020;14(1):39-46.
59. Bharucha AE, Lacy BE. Mechanisms, evaluation, and management of chronic constipation. *Gastroenterology.* 2020;158(5):1232-1249.e3.

60. Bharucha AE, Pemberton JH, Locke GR. American Gastroenterological Association technical review on constipation. *Gastroenterology.* 2013;144(1):218-238.
61. Di Palma JA, Cleveland MV, McGowan J, et al. A randomized, multicenter, placebo-controlled trial of polyethylene glycol laxative for chronic treatment of chronic constipation. *Am J Gastroenterol.* 2007;102(7):1436-1441.
62. Migeon-Duballet I, Chabin M, Gautier A, et al. Long-term efficacy and cost-effectiveness of polyethylene glycol 3350 plus electrolytes in chronic constipation: a retrospective study in a disabled population. *Curr Med Res Opin.* 2006;22(6):1227-1235.
63. Awad RA, Camacho S. A randomized, double-blind, placebo-controlled trial of polyethylene glycol effects on fasting and postprandial rectal sensitivity and symptoms in hypersensitive constipation-predominant irritable bowel syndrome. *Colorectal Dis.* 2010;12(11):1131-1138.
64. Chapman RW, Stanghellini V, Geraint M, et al. Randomized clinical trial: macrogol/PEG 3350 plus electrolytes for treatment of patients with constipation associated with irritable bowel syndrome. *Am J Gastroenterol.* 2013;108(9):1508-1515.
65. Grover M, Drossman DA. Centrally acting therapies for irritable bowel syndrome. *Gastroenterol Clin N Am.* 2011;40(1):183-206.
66. Chey WD, Lembo AJ, Rosenbaum DP. Efficacy of tenapanor in treating patients with irritable bowel syndrome with constipation: a 12-week, placebo-controlled phase 3 trial (T3MPO1). *Am J Gastroenterol.* 2020;115(2):281-293.
67. Ibsrela [package insert]. Fremont, CA: Ardelyx, Inc; 2019.
68. Amitiza [package insert]. Bedminster, NJ: Sucampo Pharma Americas, LLC; 2019.
69. Linzess [package insert]. Madison, NJ: Allergan USA, Inc; 2018.
70. Trulance [package insert]. Bridgewater, NJ: Salix Pharmaceuticals, a division of Bausch Health, US, LLC; 2020.
71. Johanson JF, Morton D, Geenen J, et al. Multicenter, 4-week, double-blind, randomized, placebo-controlled trial of lubiprostone, a locally-acting type-2 chloride channel activator, in patients with chronic constipation. *Am J Gastroenterol.* 2008;103(1):170-177.
72. Drossman DA, Chey WD, Johanson JF, et al. Clinical trial: lubiprostone in patients with constipation-associated irritable bowel syndrome - results of two randomized, placebo-controlled studies. *Aliment Pharmacol Ther.* 2009;29(3):329-341.
73. Rao SSC, Lembo A, Shiff S, et. al. A 12-week randomized, controlled trial with a 4-week randomized withdrawal period to evaluate the efficacy and safety of linaclotide in irritable bowel syndrome with constipation. *Am J Gastroenterol.* 2012;107:1714-1724.
74. Rao SSC. Update on the role of plecanatide in the treatment of chronic idiopathic constipation. *Ther Adv Gastroenterol.* 2018;11:1-14.
75. Castro J, Harrington AM, Hughes PA, et al. Linaclotide inhibits colonic nociceptors and relieves abdominal pain via guanylate cyclase-C and extracellular cyclic guanosine 3′,5′-monophoshpate. *Gastroenterology.* 2013;145(6):1334-1346.e11.
76. Hannig G, Tchernychev B, Kurtz CB, et al. Guanylate cyclase-C/cGMP: an emerging pathway in the regulation of visceral pain. *Front Mol Neurosci.* 2014;7:31.
77. Silos-Santiago I, Hannig G, Eutamene H, et al. Gastrointestinal pain: unraveling a novel endogenous pathway through uroguanylin/guanylate cyclase-C/cGMP activation. *Pain.* 2013;154(9):1820-1830.
78. Chey WD, Lembo AJ, Lavins BJ, et al. Linaclotide for irritable bowel syndrome with constipation: a 26-week, randomized, double-blind, placebo-controlled trial to evaluate efficacy and safety. *Am J Gastroenterol.* 2012;107(11):1702-1712.
79. Rao SSC, Quigley EMM, Shiff SJ, et al. Effect of linaclotide on severe abdominal symptoms in patients with irritable bowel syndrome with constipation. *Clin Gastroenterol Hepatol.* 2014;12(4):616-623.
80. Rao SSC, Xiang X, Yan Y, et al. Randomised clinical trial: linaclotide vs placebo-a study of bi-directional gut and brain axis. *Aliment Pharmacol Ther.* 2020;51(12):1332-1341.
81. Chey WD, Lembo AJ, Rosenbaum DP. Tenapanor treatment of patients with constipation-predominant irritable bowel syndrome: a phase 2, randomized, placebo-controlled efficacy and safety trial. *Am J Gastroenterol.* 2017;112(5):763-774.
82. Prichard DO, Bharucha AE. Recent advances in understanding and managing chronic constipation. *F1000Res.* 2018;7:1640.
83. Motegrity [package insert]. Shire US, Inc.: Lexington, MA; 2018.
84. Camilleri M, Piessevaux H, Yiannakou Y, et al. Efficacy and safety of prucalopride in chronic constipation: an integrated analysis of six randomized, controlled clinical trials. *Dig Dis Sci.* 2016;61(8):2357-2372.
85. Omer A, Quigley EMM. An update on prucalopride in the treatment of chronic constipation. *Ther Ad Gastroenterol.* 2017;10(11):877-887.
86. Food and Drug Administration. FDA Advisory Committee Meeting Briefing Document. Prucalopride for the treatment of chronic idiopathic constipation. https://www.fda.gov/media/119034/download. Published October 2018. Accessed September 13, 2020.
87. Tack J, Quigley E, Camilleri M, et al. Efficacy and safety of oral prucalopride in women with chronic constipation in whom laxatives have failed: an integrated analysis. *United Eur Gastroenterol J.* 2013;1:48-59.
88. Yiannakou Y, Piessevaux H, Bouchoucha M, et al. A randomized, double-blind, placebo-controlled, phase 3 trial to evaluate the efficacy, safety, and tolerability of prucalopride in men with chronic constipation. *Am J Gastroenterol.* 2015;110(5):741-748.
89. Tack J, van Outryve M, Beyens G, et al. Prucalopride (Resolor) in the treatment of severe chronic constipation in patients dissatisfied with laxatives. *Gut.* 2009;58(3):357-365.
90. Müller-Lissner S, Rykx A, Kerstens R, et al. A double-blind, placebo-controlled study of prucalopride in elderly patients with chronic constipation. *Neurogastroenterol Motil.* 2010;22(9):991-998.
91. Camilleri M, Van Outryve MJ, Beyens G, et al. Clinical trial: the efficacy of open-label prucalopride treatment in patients with chronic constipation: follow-up of patients from the pivotal studies. *Aliment Pharmacol Ther.* 2010;32(9):1113-1123.
92. Garnock-Jones KP. Prucalopride: a review in chronic idiopathic constipation. *Drugs.* 2016;76(1):99-110.
93. Pasricha PJ. Desperately seeking serotonin. A commentary on the withdrawal of tegaserod and the state of drug development for functional and motility disorders. *Gastroenterology.* 2007;132(7):2287-2290.

SUPPLEMENT TO
THE JOURNAL OF
FAMILY
PRACTICE®