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GUIDELINES

AGA Clinical Practice Guideline on the Pharmacological Management of Irritable Bowel Syndrome With Diarrhea

Anthony Lembo,[1,*] **Shahnaz Sultan**,[2,3,*] Lin Chang,[4] Joel J. Heidelbaugh,[5] Walter Smalley,[6] and G. Nicholas Verne[7]

[1]Division of Gastroenterology, Beth Israel Deaconess Medical Center, Boston, Massachusetts; [2]Division of Gastroenterology, Hepatology, and Nutrition, University of Minnesota, Minneapolis, Minnesota; [3]Veterans Affairs Healthcare System, Minneapolis, Minnesota; [4]Vatche and Tamar Manoukian Division of Digestive Diseases, David Geffen School of Medicine at University of California-Los Angeles, Los Angeles, California; [5]Department of Family Medicine, University of Michigan Medical School, Ann Arbor, Michigan; [6]Division of Gastroenterology, Vanderbilt University School of Medicine, Nashville, Tennessee; and [7]Department of Medicine, University of Tennessee College of Medicine, Memphis, Tennessee

This article has an accompanying continuing medical education activity, also eligible for MOC credit, on page e15. Learning Objective: Upon completion of this CME activity, successful learners will be able to identify pharmacologic treatment options for the management of individuals with IBS-D.

BACKGROUND & AIMS: Irritable bowel syndrome (IBS) is a common functional gastrointestinal disorder associated with significant disease burden. This American Gastroenterological Association Guideline is intended to support practitioners in decisions about the use of medications for the pharmacological management of IBS with predominant diarrhea (IBS-D) and is an update of a prior technical review and guideline. **METHODS:** The Grading of Recommendations Assessment, Development and Evaluation framework was used to assess evidence and make recommendations. The technical review panel prioritized clinical questions and outcomes according to their importance for clinicians and patients and conducted an evidence review of the following agents: eluxadoline, rifaximin, alosetron, loperamide, tricyclic antidepressants, selective serotonin reuptake inhibitors, and antispasmodics. The guideline panel reviewed the evidence and used the Evidence-to-Decision Framework to develop recommendations. **CONCLUSIONS:** The panel agreed on 8 recommendations for the management of patients with IBS-D. The panel made conditional recommendations for eluxadoline, rifaximin, alosetron, (moderate certainty), loperamide (very low certainty), tricyclic antidepressants, and anstispasmodics (low certainty). The panel made a conditional recommendation against the use of selective serotonin reuptake inhibitors (low certainty).

Keywords: Irritable Bowel Syndrome; Treatment; Symptoms; Quality of Life; Randomized Controlled Trials; Meta-Analysis; Eluxadoline; Rifaximin; Alosetron; Antidiarrheals; Antispasmodics; Tricyclic Antidepressants; Selective Serotonin Reuptake Inhibitors.

This guideline is 1 of 2 related documents that provides updated evidence-based recommendations for the management of irritable bowel syndrome (IBS). Although this guideline focuses on the pharmacological management of IBS with predominant diarrhea, a separate and accompanying guideline focuses on pharmacological management of IBS with predominant constipation. Because these 2 documents serve as stand-alone guidelines that replace the prior technical review and guideline on the American Gastroenterological Association Guideline platform, sections of the documents and select recommendation statements are common to both guidelines.

Irritable bowel syndrome (IBS) is a common disorder of gut–brain interaction with a worldwide prevalence among adults between 4.1% (Rome IV criteria) and 10.1% (Rome III criteria).[1,2] IBS affects individuals regardless of race, age, or sex, but it is most common in women and younger individuals. Although not a life-threatening condition, IBS is associated with significant disease burden, including decrease in quality of life (QOL), elevated rates of psychological comorbidities, and high economic costs.[3–6] Patients with IBS have worse health-related QOL than patients with diabetes or end-stage renal disease.[7] The impact of IBS on daily functioning can be demonstrated by high rates of absenteeism (average of 13.4 days of work or school per year compared with 4.9 days for those without IBS) and presenteeism (87% report reduced productivity at work in the past week resulting in nearly 14 hours per week of lost productivity due to IBS).[8–10] Socially, the impact of IBS on daily life can be seen in the negative impact of eating outside the home, going out with friends, traveling, and going to new or unfamiliar places.[11,12]

IBS with diarrhea (IBS-D) is one of the main bowel habit subtypes of IBS, with an estimated 30%–40% of IBS cases classified as IBS-D.[1,13] A positive diagnosis of IBS-D can be

*Authors share co-first authorship.

Abbreviations used in this paper: **AGA, American Gastroenterological Association; BSFS, Bristol Stool Form Scale; FDA, US Food and Drug Administration; GRADE, Grading of Recommendations Assessments, Development, and Evaluation; IBS, irritable bowel syndrome; IBS-C, irritable bowel syndrome with constipation; IBS-D, irritable bowel syndrome with diarrhea; QOL, quality of life; RCT, randomized controlled trial; RR, relative risk; SOS, Sphincter of Oddi spasm; TR, technical review.**

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made on the basis of medical history and physical examination, evaluation of gastrointestinal symptoms (especially alarm signs), limited diagnostic testing,[14,15] and use of the symptom-based Rome IV criteria.[16] The presence of alarm features, such as new symptom onset after age 50 years; rectal bleeding not attributable to hemorrhoids or anal fissures; unintentional weight loss; iron deficiency anemia; nocturnal diarrhea; and a family history of colon cancer, inflammatory bowel disease, or celiac disease, requires more patient-specific investigations.

Objective

Since the American Gastroenterological Association (AGA) published the first IBS technical review (TR) and guidelines in 2014,[17,18] new pharmacological treatments have become available and new evidence has accumulated about established treatments. The purpose of these guidelines is to provide evidence-based recommendations for the pharmacological management of individuals with IBS-D based on a systematic and comprehensive synthesis of the literature. In addition, we included the recommendations for the following 3 classes of pharmacotherapeutic agents for IBS: tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), and antispasmodics, not specific to one bowel subtype, which were included in the prior TR and guidelines.[17,18] Updated evidence-based recommendations for IBS with constipation (IBS-C) are available in a separate guideline.

Target Audience

The target audience of these guidelines includes primary care and gastroenterology health care professionals, patients, and policy makers. These guidelines are not intended to impose a standard of care, rather they provide the basis for rational informed decisions for patients and health care professionals. Statements regarding the underlying values and preferences, as well as qualifying remarks accompanying each recommendation, should never be omitted when quoting or translating recommendations from these guidelines. Recommendations provide guidance for typical patients with IBS-D; no recommendation can consider all of the unique individual circumstances that must be accounted for when making recommendations for individual patients. However, discussions around benefits and harms can be used for shared decision making, especially for conditional recommendations when patient values and preferences are important to consider. These recommendations are summarized in Table 1 (Executive Summary of Recommendations).

Methods

Overview

This document represents the official recommendations of the AGA and was developed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework. and adheres to best practices in guideline development, as outlined previously by the National Academy of Medicine (formerly Institute of Medicine). Development of this guideline was fully funded by the AGA Institute.[19]

Guideline Panel Composition and Conflict of Interest

Members of the guideline and TR panels were selected on the basis of their clinical and methodological expertise after undergoing a vetting process that required disclosing all conflicts of interest. The TR panel consisted of 2 content experts with expertise in IBS (A.L., L.C.) and a guideline methodologist with expertise in evidence synthesis and GRADE (S.S.). This guideline was developed by a multidisciplinary panel that included a family medicine practitioner (J.H.), general gastroenterologist (W.S.), gastroenterologist with expertise in IBS (G.N.V.), and a guideline methodologist (S.S.). Panel members disclosed all potential conflicts of interest. Conflicts were managed according to AGA policies, the National Academy of Medicine and Guidelines International Network standards, and stored with AGA. The methodologist had no conflict of interest. No guideline panel members were excused from participation in the process owing to disqualifying conflict.

Scope

The guideline panel and TR team identified and formulated clinically relevant questions focused on pharmacological therapies for IBS-D. As this was an update of a prior IBS guideline published in 2014,[17,18] the authors identified new clinical questions and reviewed the evidence for pharmacological therapies from the prior guideline. This guideline provides new or updated recommendations for the following pharmacological therapies for IBS: eluxadoline, rifaximin, and a review of the evidence and recommendations for alosetron and loperamide. In addition, we included recommendations for 3 classes of pharmacotherapeutic agents for IBS (TCAs, SSRIs, and antispasmodics) that are not specific to one IBS bowel subtype and were included in the prior TR and guidelines.[17,18]

Formulation of Clinical Questions and Determining Outcomes of Interest

A protocol was developed *a priori* by the TR panel to guide the systematic review. The PICO format was used to outline the specific patient population (P), intervention (I), comparator (C), and outcome(s) for each clinical question. We focused on adults (aged 18 years and older) with IBS using symptom-based diagnostic criteria. The panel selected desirable (benefits) and undesirable (harms) patient-important outcomes that were consistent with the prior technical review. Only CRITICAL and IMPORTANT outcomes (for decision making) were summarized in the evidence profiles. The US Food and Drug Administration (FDA) responder end point for IBS-D was considered to be a CRITICAL outcome. This was defined as a participant who reports both a $\geq$30% reduction in average daily worst abdominal pain scores and a $\geq$50% reduction in number of days per week with at least 1 stool that has a consistency of type 6 or 7 according to the Bristol Stool Form Scale (BSFS)[20] compared with baseline. The European Medicines Agency responder end point was similar to the FDA responder end point except it was for $\geq$13 of 26 weeks. The

Table 1. Executive Summary of Recommendations

New or updated recommendations[a]	Strength of recommendation	Certainty in evidence
1. In patients with IBS-D, the AGA suggests using eluxadoline Implementation remark: eluxadoline is contraindicated in patients without a gallbladder or those who drink more than 3 alcoholic beverages per day	Conditional	Moderate
2a. In patients with IBS-D, the AGA suggests using rifaximin	Conditional	Moderate
2b. In patients with IBS-D with initial response to rifaximin who develop recurrent symptoms, the AGA suggests retreatment with rifaximin	Conditional	Moderate
3. In patients with IBS-D, the AGA suggests using alosetron	Conditional	Moderate
4. In patients with IBS-D, the AGA suggests using loperamide	Conditional	Very low
5. In patients with IBS, the AGA suggests using TCAs	Conditional	Low
6. In patients with IBS, the AGA suggests against using SSRIs	Conditional	Low
7. In patients with IBS, the AGA suggests using antispasmodics	Conditional	Low

[a]For all recommendation statements, the comparator was no drug treatment.

following outcomes were considered IMPORTANT outcomes: abdominal pain response, complete spontaneous bowel movement response, improvement in IBS-QOL, improvement in stool consistency, urgency, and bloating. Undesirable outcomes included adverse effects leading to treatment discontinuation. For IBS-QOL score, the range is 0 to 100 and a minimal important difference is 14.[21] No minimal clinical important threshold has been established for improvement in stool consistency, urgency, or bloating. The minimal clinically meaningful improvement (often referred to as the smallest difference that patients care about) was defined as an improvement in an outcome of $\geq$10% by the authors (consistent with the prior TR[17]). This threshold was used to make contextualized judgments about imprecision.

Search Strategy

An experienced medical librarian conducted a comprehensive search of the following databases (Ovid Medline In-Process & Other Non-Indexed Citations, Ovid MEDLINE, EMBASE, and Wiley Cochrane Library) from inception to April 21, 2020, using a combination of controlled vocabulary terms supplemented with keywords (see Supplementary Figure 1). To ensure that recent studies were not missed, searches were updated before external review. The search was limited to English language and human adults. The bibliography of prior guidelines and the included references were searched to identify relevant studies that may have been missed. In addition, content experts helped identify any ongoing studies.

Study Selection, Data Collection, and Analysis

The inclusion and exclusion criteria were based on the formulated clinical questions. Only randomized controlled trials (RCTs) conducted in adults with IBS evaluating interventions of interest were considered. The title and abstract of each identified reference were reviewed by 1 investigator (S.S.). Each full-text article was evaluated by all members of the TR team; any question or uncertainty was resolved by means of discussion with the team. If results were incomplete or unclear, study authors or study sponsors were contacted for additional information. Outcomes were abstracted and reported as failure of symptom relief (FDA responder), failure of abdominal pain response, failure of improvement in stool consistency, bloating or urgency, failure to achieve a clinically meaningful improvement in IBS-QOL, and adverse events leading to treatment discontinuation. For rifaximin retreatment, 2 additional outcomes were also included: failure to prevent recurrence and failure of a durable response. Pooled relative risk (RR) or odds ratios and 95% CIs were calculated using the Mantel-Haenszel fixed-effects model (in the absence of heterogeneity and if fewer than 3 studies) or the DerSimonian-Liard random-effects model.[22] Statistical heterogeneity was assessed using the I^2 statistic. Direct comparisons were performed using RevMan, version 5.3 (Cochrane Collaboration, Copenhagen, Denmark). To ensure that recent studies were not missed, searches were updated before external review. See Supplementary Figure 2 for the Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram.

Certainty of the Evidence

Risk of bias was assessed using the Cochrane Risk-of-Bias Tool for RCTs and the certainty of evidence was assessed using the GRADE approach.[19] The certainty of evidence reflects the extent of our confidence in the estimates of effect. Evidence from RCTs start as high certainty, and evidence derived from observational studies start as low certainty. For each outcome, the evidence is graded as high, moderate, low, or very low (Table 2). The evidence can be rated down for risk of bias, inconsistency, indirectness, imprecision, and publication bias. The certainty of evidence originating from observational studies can be rated up when there is a large magnitude of effect or dose–response relationship. Judgments about the certainty of evidence were determined via consensus and an overall judgment of certainty of evidence was made for each PICO. Evidence profiles were developed using the GRADEpro

Table 2. Interpretation of Strong and Conditional Recommendations Using the Grading of Recommendations Assessments, Development and Evaluation Approach

Implications	Strong recommendation	Conditional recommendation
For patients	Most individuals in this situation would want the recommended course of action and only a small proportion would not.	The majority of individuals in this situation would want the suggested course of action, but many would not.
For clinicians	Most individuals should receive the intervention. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.	Different choices will be appropriate for individual patients consistent with his or her values and preferences. Use shared decision making. Decision aids may be useful in helping patients make decisions consistent with their individual risks, values, and preferences.
For policy makers	The recommendation can be adapted as policy or performance measure in most situations	Policy making will require substantial debate and involvement of various stakeholders. Performance measures should assess whether decision making is appropriate.

NOTE. Strong recommendations are indicated by statements that lead with "we recommend" and conditional recommendations are indicated by statements that lead with "we suggest."

Guideline Development Tool and created evidence profiles for each question.[23] For therapies where no new evidence was identified, the evidence is summarized from the prior TR and guideline.

Evidence to Recommendations

The guideline and TR panels met face to face to discuss the evidence and the guideline authors subsequently formulated the guideline recommendations. Based on the Evidence-to-Decision Framework, the panels considered the certainty of evidence, balance of benefit and harms, patient values and preferences, and (when applicable) feasibility, acceptability, equity, and resource use. For all recommendations, the panel reached consensus. The certainty of evidence and the strength of recommendation are provided for each clinical question. As per GRADE methodology, recommendations are labeled as "strong" or "conditional." The phrase "we recommend" indicates strong recommendations and "we suggest" indicates conditional recommendations. Table 3 provides the suggested interpretation of strong and weak recommendations for patients, clinicians, and health care policy makers. For all of the recommendations, the intervention is compared with "not using the intervention" or the treatment is recommended or suggested "over no drug treatment." The comparator is not explicitly included in the recommendation statement to avoid redundancy.

Review Process

This guideline was submitted for public comment and internal review and was approved by the AGA Governing Board.

Recommendations

A summary of all of the recommendations is provided in Table 1. A description of included studies is provided in Tables 4 and 5 and an overview of the relative and absolute effect estimates for the critical outcomes is provided in Table 6. For all recommendations in this document, the pharmacological agent was compared with "no drug treatment."

Table 3. Interpretation of the Certainty in Evidence of Effects Using the Grading of Recommendations Assessments, Development and Evaluation Approach

Certainty of evidence	Definition
High ⨁⨁⨁⨁	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate ⨁⨁⨁◯	We are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low ⨁⨁◯◯	Our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.
Very low ◯◯◯◯	We have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect

Table 4. Study Characteristics and Relevant Patient-Important Outcomes

Study and setting	Patients	Intervention	Symptom relief (FDA responder)	Global symptoms	Abdominal pain	Stool consistency	Urgency	IBS-QOL
Eluxadoline for IBS-D Lembo[26] 2016 IBS-3001 n = 1282 IBS-3002 n = 1146 295 sites (269 United States, 9 Canada, 17 UK sites)	Outpatients (aged 18–80 y) with IBS-D (Rome III)[a]	Eluxadoline 75 mg or 100 mg	Reduction of ≥30% from average baseline score for worst abdominal pain and, on the same days, a stool consistency score of <5) for ≥50% of the days[b]	A score of 0 or 1, or an improvement of ≥2 over the baseline score, on ≥50% of days	Reduction of ≥30% from baseline in the score for the worst abdominal pain on ≥50% of days	Stool consistency score of <5, or the absence of a bowel movement if accompanied by an improvement of ≥30% in the score for the worst abdominal pain, on ≥50% of days	≥50% urgency-free days over the initial 12 wk	Change from baseline in the IBS-QOL questionnaire score

[a]Outpatients with, at baseline, average score for worst abdominal pain >3, average score for stool consistency >5.5 on BSFS, a score of ≥5 on the BSFS for at least 5 days, and an average IBS-D global symptom score ≥2.
[b]If no bowel movement, an improvement of at least 30% in the score for worst abdominal pain was sufficient.

Table 5. Rifaximin Retreatment: Study Characteristics and Relevant Patient-Important Outcomes[a]

Study and setting	Patients	Intervention	Symptom relief (FDA responder)	Prevention of recurrence	Durable response	Abdominal pain	Stool consistency	Bloating	Urgency	IBS-QOL
Rifaxiimin for IBS-D Lembo[26] 2016 270 centers in the United States, United Kingdom, and Germany	Outpatients (aged ≥18 y) with IBS-D (Rome III) classified as responders to the initial open-label rifaximin treatment who then experienced a relapse in IBS-D symptoms (defined as a loss of treatment response for either weekly abdominal pain or stool consistency for ≥3 wk	Rifaximin 550 mg tid for 14 d 2 repeat treatment courses (the second repeat treatment course was initiated 10 wk after completion of the first repeat treatment course)	Reduction of ≥30% from average baseline score for worst abdominal pain and, on the same days, a stool consistency score of <5) for ≥50% of the days[b]	Responder who did not have recurrence through the end of the 6-wk repeat treatment observation phase and continued to respond without recurrence through the end of the second repeat treatment phase	Also called "sustained IBS symptom relief" responder who did not have recurrence through the 6-wk repeat treatment observation phase	Reduction of ≥30% from baseline in the score for the worst abdominal pain on ≥50% of days	Decrease of ≥50% of days/week with BSFS type 6 or 7 stools)	≥1-point decrease from baseline in weekly average bloating score[b] for ≥2 of the 4-wk after treatment	≥30% improvement from baseline in the percentage of days with urgency for ≥2 wk during the 4 wk after treatment	Change from baseline in the IBS-QOL questionnaire score

[a]Study design: Patients meeting eligibility criteria entered into the open-label treatment phase, which consisted of rifaximin 550 mg tid for 2 weeks, followed by a 4-week assessment period to determine response. Responders to open-label rifaximin were then monitored in an observation phase for up to an additional 18 weeks or until symptom relapse occurred. Patients who failed to meet the prespecified weekly response criteria for both abdominal pain and stool consistency after the initial open-label rifaximin treatment were classified as nonresponders and withdrawn from the trial. Patients who were classified as responders to the initial open-label rifaximin treatment and who experienced a relapse in IBS-D symptoms for ≥3 weeks of a consecutive, rolling 4-week period during the 18-week observation phase) entered into the double-blind treatment phase of the trial, in which patients were randomly assigned (1:1) to receive 2 repeat treatment courses of rifaximin 550 mg tid or placebo tid for 14 days. Response to repeat treatment was assessed during the 4 weeks immediately after repeat treatment. The primary evaluation period for the trial was the 4-week follow-up period after the first repeat treatment. However, all patients, regardless of response or relapse status after the first repeat treatment, received a second repeat treatment with the same treatment assigned at randomization (ie, rifaximin 550 mg or placebo tid for 14 days). The second repeat treatment course was initiated 10 weeks after completion of the first repeat treatment course (ie, after the 4-week primary evaluation period and 6-week repeat treatment observation phase).
[b]How bothersome was your IBS-related bloating in the last 24 hours? 0 = not at all; 1 = hardly; 2 = somewhat; 3 = moderately; 4 = a good deal; 5 = a great deal; 6 = a very great deal.

Table 6. An Overview of the Effect Estimates for the Newer Pharmacological Agents

Critical outcomes	No. of participants (studies)	RR (95% CI)	Absolute effects (95% CI)	Certainty of evidence
Eluxadoline 12-wk data				
Failure of symptom relief (FDA responder definition)	1617 (2 RCTs)	0.87 (0.83–0.92)	108 fewer per 1000 (from 67 fewer to 142 fewer)	⨁⨁⨁◯ MODERATE
Pancreatitis	2474 (2 RCTs)	Not estimable	3 more per 1000 (from 0 more to 6 more)	⨁⨁⨁⨁ HIGH
Sphincter of Oddi dysfunction	2474 (2 RCTs)	Not estimable	5 more per 1000 (from 1 more to 8 more)	⨁⨁⨁⨁ HIGH
Rifaximin retreatment				
Failure of symptom relief (30% response in improvement in abdominal pain and stool consistency) for at least 2 of 4 wk after treatment (equivalent to FDA end point)	636 (1 RCT)	0.90 (0.80–1.01)	69 fewer per 1000 (from 7 more to 137 fewer)	⨁⨁⨁◯ MODERATE
Failure to prevent recurrence	578 (1 RCT)	0.93 (0.88–0.99)	65 fewer per 1000 (from 9 fewer to 112 fewer)	⨁⨁⨁◯ MODERATE
Failure of a durable response	636 (1 RCT)	0.94 (0.88–1.00)	53 fewer per 1000 (from 0 fewer to 106 fewer)	⨁⨁⨁◯ MODERATE
Drug-related AEs (important outcome)	636 (1 RCT)	0.70 (0.25–2.01)	8 fewer per 1000 (from 19 fewer to 26 more)	⨁⨁⨁◯ MODERATE

AE, adverse event.

1. Should Eluxadoline Be Used in Patients With Irritable Bowel Syndrome With Diarrhea?

The AGA suggests using eluxadoline in patients with IBS-D.
(Conditional recommendation, moderate certainty)
Implementation remark: Eluxadoline is contraindicated in patients without a gallbladder or those who drink more than 3 alcoholic beverages per day.

Eluxadoline is a minimally absorbed mixed μ- and κ-opioid receptor agonist and δ-opioid receptor antagonist that was developed to reduce constipation and increase analgesic potency compared with pure μ-opioid agonist.[24,25] Eluxadoline is FDA-approved for the treatment of IBS-D at a dosage of 100 mg twice daily. Eluxadoline 75 mg twice daily is recommended in patients who are unable to tolerate the 100-mg dose, who have mild or moderate hepatic impairment, or who are receiving concomitant OATP1B1 inhibitors. Eluxadoline is contraindicated in patients without a gallbladder or those who drink more than 3 alcoholic beverages per day.

Summary of the evidence. In 2 large phase 3 trials, eluxadoline 75 and 100 mg twice daily were assessed over 26 weeks in patients with IBS-D.[26] Patients were eligible if they met Rome III criteria for IBS-D[27] and had an average worst abdominal pain score of $\geq$3 (on a scale of 0–10, with 0 indicating no pain and 10 the worst imaginable pain), an average score for stool consistency of $\geq$5.5 on the BSFS,[20] a BSFS score of $\geq$5 for at least 5 days, and an average IBS-D global symptom score of $\geq$2 (on a scale of 0–4, with 0 indicating no symptoms and 4 indicating very severe symptoms). Exclusion criteria included a history of pancreatitis and Sphincter of Oddi spasm (SOS), alcohol abuse, and post-cholecystectomy biliary pain.

Benefits. In the 2 phase 3 trials, 808 patients with IBS-D were randomized to receive eluxadoline at 100 mg and 809 were given placebo twice daily.[26] Compared with placebo, a greater proportion of patients who received eluxadoline were FDA end point responders (27.2% vs 16.7%; RR, 0.87; 95% CI, 0.83–0.92) and European Medicines Agency end point responders (30.9% vs 19.5%; RR, 0.86; 95% CI, 0.81–0.91). These studies also used a global assessment measuring adequate relief of IBS-D symptoms. Compared with placebo, a greater proportion of patients who received eluxadoline reported adequate relief for $\geq$6 of the first 12 weeks (38.4% vs 29.2%; RR, 0.87; 95% CI, 0.81–0.93).

With respect to individual symptoms, during the initial 12 weeks, eluxadoline may be associated with an improvement in abdominal pain (RR, 0.92; 95% CI, 0.84–1.00). Compared with placebo, eluxadoline was associated with a greater proportion of responders for the outcomes of stool consistency (RR, 0.84; 95% CI, 0.80–0.88) and $\geq$50% urgency-free days (RR, 0.84; 95% CI, 0.78–0.90). Finally, a greater proportion of patients receiving eluxadoline achieved a clinically meaningful improvement in IBS-QOL compared with placebo during the initial 12 weeks (RR, 0.84; 95% CI, 0.74–0.95). Similar results for all outcomes were seen at week 26.

Adverse events. The most common adverse events in patients taking eluxadoline were constipation (8%), nausea (7%), and abdominal pain (7%). The rates of

discontinuation due to adverse events were approximately 8% and 4% in patients treated with eluxadoline and placebo, respectively. There were 5 pancreatitis (RR, –5.34; 95% CI, 0.30–96.42) and 8 SOS events in patients treated with eluxadoline (RR, 8.25; 95% CI, 0.48–142.76) and none in those receiving placebo. These cases were associated with the absence of a gallbladder or history of alcohol abuse. For this reason, eluxadoline is contraindicated in patients without a gallbladder or those who drink more than 3 alcoholic beverages per day.

Certainty in evidence of effects. The panel rated down for imprecision across many of the outcomes because the lower boundary of the CI crossed our threshold of a clinically meaningful difference and the range of possible effects included benefits that may not be meaningful to patients. The overall certainty in evidence of effects for eluxadoline was MODERATE**.** See Supplementary Tables 1 and 2 for the full evidence profile.

Rationale. The panel made a conditional recommendation for eluxadoline in patients with IBS-D after weighing the benefits and adverse events. Evidence supporting the efficacy of 100 mg of eluxadoline in IBS-D based on 2 phase 3 RCTs.[26] Although eluxadoline was associated with a significantly greater proportion of patients meeting the FDA end point for IBS-D and also adequate global relief of IBS symptoms compared with placebo, the improvement may be small in some patients. Although eluxadoline was associated with clinically meaningful improvements in stool consistency and urgency, it had less effect on abdominal pain. Thus, eluxadoline may be more ideal in patients with IBS-D with predominant and bothersome diarrhea than in those with predominant or more severe abdominal pain. The symptom benefits of eluxadoline translated to a significant proportion of patients reporting clinically significant improvement in IBS-QOL. Eluxadoline 100 mg twice daily is the generally recommended dose in most patients, although very similar beneficial effects were found with the 75-mg dose of eluxadoline. Eluxadoline is associated with an increased risk of pancreatitis (in patients without a gallbladder) and SOS (in patients with a history of alcohol abuse). Thus, eluxadoline is contraindicated in patients without a gallbladder and excessive alcohol abuse, as well as a history of Sphincter of Oddi disease or SOS, pancreatitis, bile duct obstruction, and severe liver impairment.[28]

2. Should Rifaximin Be Used for Patients With Irritable Bowel Syndrome With Diarrhea for Initial Treatment and Retreatment?

2a. The AGA suggests using rifaximin in patients with IBS-D.
(Conditional recommendation, moderate certainty)
2b. In patients with IBS-D with an initial response to rifaximin who develop recurrent symptoms, the AGA suggests retreatment with rifaximin.
(Conditional recommendation, moderate certainty)

Rifaximin is a nonabsorbable, oral antibiotic with a broad spectrum of activity against both gram-negative and gram-positive anaerobic and aerobic bacteria. It is FDA-approved for treatment of IBS-D at a dosage of 550 mg 3 times per day for 14 days. Patients who experience a recurrence of symptoms can be retreated up to 2 times with the same dosage regimen.

Summary of the evidence for treatment with rifaximin. The 2014 TR[17] examined 3 RCTs in 1258 patients (rifaximin n = 624; placebo n = 634), which compared rifaximin with placebo for the treatment of nonconstipated, Rome II–positive IBS patients.[29–31] Efficacy end points were assessed during the 4 weeks after completing 2 weeks of treatment with rifaximin. The FDA responder end point for IBS-D was evaluated only in the 2 phase 3 clinical trials. Compared with placebo, rifaximin had a significantly greater response based on the FDA responder end point for IBS-D (RR, 0.85; 95% CI, 0.78–0.94). Compared with placebo, rifaximin was also superior with respect to adequate relief of global relief and discomfort (RR, 0.87; 95% CI, 0.80–0.94). In the phase 3 trials, rifaximin was associated with greater improvement in relief of bloating (RR, 0.86; 95% CI, 0.70–0.93) and abdominal pain (RR, 0.87; 95% CI, 0.80–0.95). Outcomes including spontaneous bowel movement and complete spontaneous bowel movement responder rates, health-related QOL improvement, and diarrhea leading to treatment withdrawal could not be assessed based on the available data at that time. During the 10-week follow-up period, the percentage of patients who were responders taking rifaximin or placebo diminished similarly over time. In an effort to evaluate the post-treatment effect of rifaximin beyond the 10 weeks of these pivotal RCTs, a subsequent placebo-controlled, 51-week, phase 3 RCT was conducted to assess the efficacy and safety of repeat treatment after clinical response and subsequent symptom relapse with rifaximin for IBS-D.[26]

Summary of the evidence for retreatment with rifaximin. In the phase 3 retreatment trial with rifaximin,[26] patients with IBS-D who met Rome III diagnostic criteria[31] and had baseline abdominal pain and bloating scores of ≥3 (on a scale of 0–10, with 0 indicating no pain and 10 indicating the worst imaginable pain) and loose stools of ≥2 days per week (ie, BSFS[20] type 6 or 7) were enrolled. A single-blind, baseline screening phase of placebo for 10 days was conducted to remove placebo responders. Patients then entered an open-label treatment phase with rifaximin 550 mg 3 times daily for 2 weeks. As in the 2 previous phase 3 trials, a responder was defined as simultaneous improvement in both abdominal pain (≥30% decrease from baseline in pain score) and stool consistency (≥50% increase from baseline in number of days per week with BSFS type 6 or 7) during ≥2 of the 4 weeks after treatment. This end point is equivalent to the FDA end point for IBS-D, although only for 4 weeks. Responders were observed for up to 18 additional weeks or until symptom relapse occurred. Relapse was defined as a loss of treatment response for either weekly abdominal pain (≤30% decrease from baseline in mean weekly pain score) or stool consistency (≤50% decrease from baseline in number of days per

week with BSFS type 6 or 7 stool) for ≥3 of 4 consecutive weeks. Responders who relapsed were randomized to either two 14-day repeat treatment courses of rifaximin at 550 mg 3 times daily or placebo for 2 weeks separated by 10 weeks.

The primary end point of this study was the percentage of FDA end point responders during the 4 weeks after the first repeat treatment (primary evaluation period). The primary end point was considered a CRITICAL outcome. Three additional CRITICAL end points were prevention of recurrence, sustained IBS symptom relief ("durable" response), and bloating response.[26] IMPORTANT outcomes were adequate relief of abdominal pain, adequate relief of urgency improvements in stool consistency, and percentage of patients with a clinically meaningful improvement in IBS-QOL.[21,32]

Benefits. There were 2438 patients with IBS-D who completed 2 weeks of rifaximin treatment in the open-label phase. Of the 1074 patients (44.1%) who responded to open-label rifaximin, 382 (35.6%) did not relapse within the 18-week follow-up period. Of the 692 (64.4%) who did relapse, 636 were randomized to the first repeat treatment phase of the trial with 328 patients randomized to rifaximin and 308 to placebo 3 times daily for 14 days. A higher proportion of patients who received rifaximin were responders compared with those who received placebo (38.1% vs 31.5%; RR, 0.90; 95% CI, 0.80–1.01). A greater proportion of patients treated with rifaximin did not experience symptom recurrence up to 10 weeks after the first retreatment (durable response) than patients on placebo (17.1% vs 11.7%; RR, 0.94; 95% CI, 0.88–1.00) or throughout the retreatment phase of the study (13.2% vs 7.1%; RR, 0.93; 95% CI, 0.88–0.99).

A greater proportion of patients with IBS-D taking rifaximin achieved adequate relief of abdominal pain compared with patients taking placebo (50.6% vs 42.2%; RR, 0.85; 95% CI, 0.74–0.99). Compared with placebo, rifaximin was also associated with a greater proportion of patients reporting adequate improvement in urgency (48.5% vs 39.6%; RR, 0.85; 95% CI, 0.74–0.98). Improvements in stool consistency (51.8% vs 50%; RR, 0.85; 95% CI, 0.82–1.13) and bloating (46.6% vs 41.2%; RR, 0.85; 95% CI, 0.79–1.04) were similar between rifaximin and placebo. Patients taking rifaximin were also more likely to achieve a clinically meaningful improvement in IBS-QOL compared with placebo (38.7% vs 29.5%; RR, 0.66; 95% CI, 0.48–0.92).

Adverse events. Safety data from the retreatment study were reported for the open-label cohort and the double-blind cohort separately. In the open-label population, adverse events were reported in 3.3% of patients taking rifaximin (85 of 2579). In the double-blind population, adverse events were reported in 1.8% of patients on rifaximin vs 2.6% on placebo. The most common adverse events were nausea, upper respiratory infection, urinary tract infection, and nasopharyngitis. Adverse events leading to study discontinuation in the double-blind phase of the study were reported by 1 patient in each treatment group. In addition, 1 patient developed *Clostridioides difficile* colitis infection 37 days after repeat treatment with rifaximin. This patient tested negative for *C difficile* toxins A and B at study entry, although this patient had a history of *C difficile* infection and had completed 10-day course of cefdinir for a urinary tract infection immediately before development of *C difficile* colitis.

Certainty in evidence of effects. The panel rated down for imprecision across many of the outcomes because the lower boundary of the CI crossed our threshold of significance and for a clinically meaningful improvement. The overall certainty in evidence of effects for rifaximin was MODERATE. See Supplementary Table 3 for the full evidence profile.

Rationale. The panel made a conditional recommendation for initial treatment with rifaximin in individuals with IBS-D and for retreatment in patients with IBS-D who had initial response but develop recurrent symptoms. Although the evidence shows that initial treatment and retreatment with rifaximin is efficacious, the improvements across many outcomes may be small and may not be clinically meaningful. The certainty in evidence for retreatment with rifaximin is similar to the phase 3 treatment trials (target 1 and 2)[29] and compares similarly with efficacy of rifaximin in the 2014 TR.[17] In the retreatment trial, rifaximin was associated with a greater durable response and prevention of symptom recurrence of symptoms compared with placebo. In addition, the efficacy of rifaximin retreatment in improving abdominal pain, urgency, and IBS-QOL was greater than placebo, but its effect on stool consistency and bloating were not. The response rates with retreatment of rifaximin and placebo were lower than what was demonstrated in the previous phase 3 treatment trials.[29,30] In addition, rifaximin has been shown in these previous trials to significantly improve bloating compared with placebo, but retreatment with rifaximin did not have a significant effect on bloating. These differences can be due to several factors. The target 1 and 2 trials measured the efficacy of an initial course of rifaximin in patients with IBS, and the retreatment trial evaluated efficacy for symptom relapse after an open label course of rifaximin. Patients had a lower severity of symptoms at the onset of the first double-blind treatment phase.[26] Furthermore, the retreatment trial was not powered to measure the bloating response. The adverse event profile of rifaximin was similar to that of placebo. This is supported by a previous study by Schoenfeld and colleagues[33] in which the safety and tolerability of rifaximin in the phase 2b and 3 RCTs in nonconstipated patients with IBS were evaluated. Patients receiving rifaximin (n = 1103) and placebo (n = 829) had a similar incidence of drug-related adverse events (12.1% vs 10.7%), serious adverse events (1.5% vs 2.2%), drug-related adverse events resulting in study discontinuation (0.8% vs 0.8%), gastrointestinal-associated adverse events (12.2% vs 12.2%), and infection-associated adverse events (8.5% vs 9.5%).

Review of evidence from the prior technical review and guideline from 2014. Evidence for the following interventions was also reviewed: alosetron, loperamide, TCAs, SSRIs, and antispasmodics.[17]

3. Should Alosetron Be Used in Patients With Irritable Bowel Syndrome With Diarrhea?

The AGA suggests using alosetron in patients with IBS-D.
(Conditional recommendation, moderate certainty)
Implementation remark: Alosetron is restricted for use in women with severe IBS-D under a risk-management program.

Alosetron is a selective 5-HT_3 antagonist with a mechanism of action that is believed to be both centrally and peripherally mediated.[34] Alosetron was originally approved by the FDA in 2000 for the treatment of IBS-D in women; however, it was voluntarily withdrawn due to serious adverse events, namely ischemic colitis and serious complications of constipation. In 2002, the FDA approved the reintroduction of alosetron but restricted its use to the treatment of severe IBS-D in women under a risk-management program.[35] The initial recommended starting dosage is 0.5 mg twice per day. If constipation occurs, patients must stop taking the medication until symptoms resolve and may be restarted on 0.5 mg once per day; however, if constipation recurs at a lower dosage, alosetron should be discontinued. If symptoms are not controlled on this dosage after 4 weeks, the dosage can be increased to 1 mg twice per day. If symptoms persist after 4 weeks despite increasing the dosage to 1 mg twice per day, alosetron should be discontinued.

Summary of the evidence. No new studies of alosetron for the management of IBS-C were identified since the 2014 TR. Evidence to support the use of alosetron comes from 8 RCTs in 4227 patients (alosetron, n = 2517; placebo, n = 1710) that compared the efficacy of alosetron with placebo in patients with nonconstipating IBS.[36–43] Seven of the 8 studies evaluated the efficacy of alosetron during a 12-week period and the remaining study was a 48-week trial. Alosetron was superior to placebo in improving global symptoms (RR, 0.60; 95% CI, 0.54–0.67) and IBS pain and discomfort (RR, 0.83; 95% CI, 0.79–0.88). In addition, the individual studies showed that alosetron was shown to improve urgency, stool consistency, and IBS-QOL. With respect to adverse events, a postmarketing study evaluating the safety of alosetron over 9 years showed that the cumulative adjudicated incidence of ischemic colitis was 1.03 cases per 1000 patient-years and the adjudicated incidence rate of serious complications of constipation was 0.25 cases per 1000 patient-years and appeared to have declined over time.[35] The overall certainty in evidence for alosetron was MODERATE.

Rationale. Alosetron is indicated in women with IBS-D who have not responded to conventional therapy and have symptoms that are severe, which is defined as 1 or more of the following: frequent and severe abdominal pain/discomfort, frequent bowel urgency or fecal incontinence, and/or disability or restriction of daily activities due to IBS. There is moderate- to high-quality evidence that alosetron improves symptoms of IBS compared with placebo, but careful selection of patients and education about the risks and benefits of alosetron are vital. Of note, the 9-year follow-up data on the postmarketing safety of alosetron under the risk management program have shown that the incidence of complications of constipation has declined, and that of ischemic colitis has remained stable.[35]

4. Should Loperamide Be Used in Patients With Irritable Bowel Syndrome With Diarrhea?

The AGA suggests using loperamide in patients IBS-D.
(Conditional recommendation, very low certainty)

Loperamide a synthetic peripheral opioid receptor agonist; it inhibits peristalsis and antisecretory activity and prolongs intestinal transit time with limited penetrance of the blood–brain barrier. It is FDA-approved for the treatment of patients with acute, chronic, and traveler's diarrhea.

Summary of the evidence. No new studies have evaluated the efficacy of loperamide in the management of patients with IBS. Two small, double-blind, placebo controlled trials have evaluated the efficacy of loperamide in patients with IBS.[44,45] Neither defined the diagnostic criteria for IBS, but excluded organic gastrointestinal disease. Compared with placebo, loperamide was associated with adequate relief of abdominal pain (RR, 0.41; 95% CI, 0.20–0.84), improvement in stool consistency (RR, 0.06; 95% CI, 0.01–0.43), and global improvement in symptoms (RR, 0.73; 95% CI, 0.29–1.86). No improvement in urgency symptoms was noted and there were no data on IBS-QOL or adverse events. The overall certainty in evidence for loperamide was VERY LOW.

Rationale. There was a lack of beneficial effect on global improvement of symptoms of IBS and urgency, although there was improvement in abdominal pain and stool consistency. Improvements in these symptoms occurred within 3–5 weeks of starting treatment and details of how this was determined were poorly described. However, this review was based on only 2 very small studies. Both studies were published in 1987 and were conducted at a time when there was less guidance on the conduct of high-quality clinical trials. Loperamide has proven efficacy in reducing diarrhea and is commonly used in IBS-D, but there is a lack of data evaluating its efficacy in relieving abdominal symptoms. It is also not clear whether loperamide should be recommended in IBS-mixed type patients when they are experiencing diarrhea. The optimal dose and method of using loperamide (eg, as needed, daily, or after a certain number of diarrheal stools) is not known and potentially can vary between patients based on their symptom patterns.

5. Should Tricyclic Antidepressants Be Used in Patients With Irritable Bowel Syndrome?

The AGA suggests using TCAs in patients with IBS. *(Conditional recommendation; Low certainty in the evidence of effects)*

This recommendation is unchanged from the 2014 IBS guideline.[18] TCAs have been used to treat IBS symptoms due to their peripheral and central (ie, supraspinal and spinal) actions, which can affect motility, secretion, and sensation. IBS and other functional gastrointestinal disorders have been redefined in Rome IV as disorders of gut–brain interactions, characterized by any combination of motility disturbance, visceral hypersensitivity, altered mucosal and immune function, altered gut microbiota, and altered central nervous system processing.[46] Consistent with this redefinition and based on the fact that TCAs and other antidepressants have physiologic effects separate from the effect on mood, these agents have been relabeled as gut–brain neuromodulators.[47]

Summary of the evidence. The efficacy of TCAs in IBS was previously evaluated in the prior TR[17] based on 8 placebo-controlled RCTs in 523 patients (TCAs n = 297; placebo n = 122).[17] All but 1 study enrolled multiple IBS bowel habit subtypes. The type of TCA studied included amitriptyline (n = 3), desipramine (n = 2), trimipramine (n = 1), imipramine (n = 1), and doxepin (n = 1). The dose of the TCA varied from 10 mg to up to 150 mg and most studies used >50 mg per day. Global assessments differed among the trials and abdominal pain response was assessed in 4 trials. Compared with placebo, TCAs were associated with global symptom relief (RR, 0.67; 95% CI, 0.54–0.82) and abdominal pain relief (RR, 0.76–0.94). However, the quality of evidence was rated down due to indirectness, risk of bias, and imprecision. Based on data from 22 clinical trials in depression (as long-term, high-quality data on adverse events with TCAs in IBS were not available), TCAs showed a significantly higher rate of withdrawals due to adverse effects compared with placebo (RR, 2.11; 95% CI, 1.35–3.28). The overall certainty in evidence for TCAs was LOW.

Rationale. TCAs were associated with greater responses of adequate relief and abdominal pain relief compared with placebo; however, only global relief response met the threshold for being clinically meaningful. The beneficial effects of TCAs on IBS symptoms appear to be independent of effects on depression and may take several weeks. Most studies evaluated higher doses of TCAs (ie, 50 mg and higher) than those used in clinical practice. There was 1 study demonstrating that amitriptyline 10 mg at bedtime had greater efficacy that placebo in patients with IBS-D.[48] TCAs have multiple actions, including inhibition of serotonin and noradrenergic reuptake and blockade of muscarinic 1, α1 adrenergic, and histamine 1 receptors.[47] These effects are beneficial (eg, reduce diarrhea and abdominal pain), but also can cause adverse events (eg, dry mouth, sedation, and constipation). Therefore, the selection of TCA should be based on the patient's symptom presentation.

6. Should Selective Serotonin Reuptake Inhibitors Be Used in Patients With Irritable Bowel Syndrome?

The AGA suggests against using SSRIs for patients with IBS.
(Conditional recommendation, low certainty in the evidence)

This recommendation is unchanged from the 2014 IBS guideline.[18] SSRIs are approved for the treatment of mood disorders, such as anxiety and depression, but are also used in clinical practice to treat chronic pain conditions. SSRIs selectively inhibit the reuptake of 5-HT at presynaptic nerve endings, which results in an increased synaptic concentration of 5-HT. The use of SSRIs in IBS has been of considerable interest because IBS is considered a gut–brain disorder and these agents have centrally mediated effects and increase gastric and intestinal motility, although they do not appear to have a major impact on visceral sensation.[47]

Summary of the evidence. The efficacy of SSRIs in IBS was studied in 7 RCTs.[48–54] Most of the studies enrolled a mixture of all 3 main bowel habit subtypes. Patients with current psychiatric disease were generally excluded. Duration of treatment ranged from 6 to 12 weeks. Different SSRIs were evaluated: fluoxetine 20 mg daily,[48,50] paroxetine 10 mg daily that could be increased,[53] paroxetine-CR 12.5–50 mg daily,[52] and 3 studies used citalopram at a starting dose of 20 mg that was increased to 40 mg daily after 2,[54] 3,[49] or 4[51] weeks. Compared with placebo, SSRIs showed possible improvement in symptom relief (RR, 0.74; 95% CI, 0.52–1.06) and in abdominal pain or discomfort; however, the upper boundary of the CI suggested worsening symptoms of global relief or abdominal pain. The certainty in evidence for this outcome was rated as low due to serious inconsistency and imprecision. Two studies compared changes in IBS-specific QOL between the SSRI and placebo groups.[51,53] One study found a significantly greater improvement in food avoidance score[53] and the other study did not detect any differences.[51] The other critical or important outcomes could not be assessed on the basis of the available data. There were no long-term data with SSRIs in IBS or depression to assess adverse events leading to treatment withdrawal.

Rationale. SSRIs did not significantly improve global symptoms or abdominal pain in IBS, although the overall certainty in evidence is low. Multiple factors, including those arising from central and peripheral processes, contribute to the severity of IBS symptoms. In some patients, SSRIs may improve the perception of overall IBS symptoms and well-being by improving gastrointestinal symptoms, coexistent alterations in mood, and extraintestinal symptoms.[55] It is

possible that serotonin-norepinephrine reuptake inhibitors may have a greater effect on abdominal pain in IBS due to their effects on both serotonin and norepinephrine reuptake. Serotonin-norepinephrine reuptake inhibitors have been shown to be efficacious in other pain conditions, but clinical trials in IBS are lacking.[47]

7. Should Antispasmodics Be Used in Patients With Irritable Bowel Syndrome?

The AGA suggests using antispasmodics in patients with IBS.
(Conditional recommendation, low certainty in the evidence)

This recommendation is unchanged from the 2014 IBS guideline.[18] Antispasmodics are commonly used in clinical practice to reduce abdominal pain associated with IBS. Although a pharmacologically diverse class, antispasmodics are thought to relieve IBS symptoms by reducing smooth muscle contraction and possibly visceral hypersensitivity.[56] Of the antispasmodics studied, only hyoscine, dicyclomine, and peppermint oil are available in the United States.

Summary of evidence. This was based on a Cochrane Review that included 22 RCTs evaluating 2983 patients with IBS (antispasmodics, n = 1008; placebo, n = 1975).[57] Twelve different antispasmodics were assessed. There was considerable variation between the studies concerning diagnostic and inclusion criteria, dosing schedule, and study end points. Compared with placebo, there were a significantly greater proportion of patients taking antispasmodics who had adequate global relief of IBS symptoms (RR, 0.67; 95% CI, 0.55–0.80). The overall certainty in evidence, however, was low due to the serious risk of bias and publication bias. Likewise, compared with placebo, antispasmodics showed improvement in abdominal pain (RR, 0.74; 95% CI, 0.59–0.93). For this outcome, the certainty in evidence was very low due to risk of bias, publication bias, and imprecision (the upper boundary of the CI did not cross our minimal clinically important threshold). The effect of individual antispasmodics was difficult to interpret due to the small number of studies evaluated for each of the drugs. The most common adverse events reported were dry mouth, dizziness, and blurred vision, but no serious adverse events were reported. We did not include adverse events leading to discontinuation due to the lack consistent reporting.

Rationale. Antispasmodics include a wide array of pharmacological therapies that been used clinically for many years but have not been subjected to rigorous large multicenter trials. There was considerable variation among the trials and the quality of the studies was generally low. However, antispasmodics were significantly associated with a greater relief of global symptoms and abdominal pain, although the latter did not meet our criteria for being clinically meaningful. A Cochrane Review[57] found a beneficial effect for antispasmodics over placebo for improvement in abdominal pain and global assessment. It is not clear whether antispasmodics are more efficacious in specific IBS subtypes, but its regular use in constipation may be limited due to its anticholinergic effects. Although these medications are often recommended for treatment of postprandial symptoms in IBS, this has not been specifically studied in RCTs.

Limitations and Evidence Gaps

A continued unmet need in IBS clinical trials is the lack of a biomarker that can embody the different pathophysiologic mechanisms of IBS or that can reliably predict treatment response to medications that have different predominant mechanisms of action (eg, normalizing bowel habits and visceral analgesic) and a need for clinically effective treatments that relieve multiple symptoms. Dietary modification and behavioral treatments have shown beneficial effects in patients with IBS and should be considered on an individual basis, as these may be used in conjunction with pharmacological therapies. The efficacy of these interventions alone or in conjunction with pharmacological therapies was outside the scope this guideline. A recent AGA guideline on probiotics highlighted the evidence gaps in the use of probiotics in patients with IBS and concluded that future, larger, and high-quality studies are needed.[58] In addition, studies evaluating the synergistic effects of combined treatment in IBS, which is often used in patients with moderate to severe symptoms in clinical practice, and better comparative effectiveness studies in IBS are needed.

Additional considerations related to the diagnostic criteria for IBS and use of specific outcomes are outlined below.

- In 2016, the Rome IV diagnostic criteria for IBS were published, which differ from the Rome III criteria[31] in that abdominal discomfort has been deleted from the definition and abdominal pain now is required to be present at least 1 day per week on average during the preceding 3 months.[27] Based on these changes, fewer individuals meet the Rome IV criteria for IBS compared with the Rome III criteria.[59] However, for the purpose of RCTs in IBS, which generally measure changes in abdominal pain, the Rome IV criteria are more applicable. However, it is conceivable that the Rome III–positive study populations that qualified for enrollment into RCTs had symptoms that also met Rome IV criteria because a certain level of baseline symptom severity is required to show a symptom benefit.[60] Nonetheless, it is not known whether these changes to the IBS diagnostic criteria would alter the efficacy and safety of IBS treatments in RCTs.

- Responder definitions have varied in multicenter IBS RCTs until the establishment of FDA composite primary end points for IBS-C in 2012,[61] which now allows greater standardization of the efficacy of IBS treatments than in the past. However, these end points were meant to serve as interim primary end points while a patient-reported outcome instrument was being developed, as recommended by the FDA guidance for patient-reported

outcomes.[62] An FDA-approved IBS patient-reported outcome for IBS-C was completed recently.[63] The FDA recommended enrollment criteria and interim primary end points for IBS-C but not IBS-mixed type. There continues to be a lack of studies focusing on IBS-mixed type and no consensus on the optimal primary end point for this bowel habit subgroup. With respect to therapeutic agents that target abdominal pain relief without significant effects on bowel habits, there is no established consensus on the inclusion and exclusion criteria regarding bowel symptoms and treatment that normalizes bowel habits without an effect on abdominal pain (eg, antidiarrheals and laxatives).

Implementation, Cost, and Health Equity Considerations

This guideline is helpful in outlining the newer pharmacotherapeutic agents recommended for use in managing symptoms of IBS-D. Acknowledging that multimodal treatments that include dietary and behavioral approaches in conjunction with drug therapy may provide maximal benefits and that treatment choices may be influenced by patient preferences, practitioners should engage in shared decision making with patients when choosing the best therapy. The patient–physician relationship is paramount when caring for individuals with IBS and understanding patient preferences (for adverse effect tolerability as well as cost) is valuable in choosing the right therapy. Most drugs for the treatment of IBS-D are readily available and covered by prescription drug plans, although prior authorizations may be required by some insurance companies, and the case for prescribing is strengthened when a patient has tried and failed generic therapies. Also, newer drugs may still be available in brand name formulations only, as generic formulations do not yet exist and thus out of pocket expenses for patients can vary widely depending on prescription coverage with various insurance plans. Some patient assistance programs exist that can offset drug costs. The guideline, clinical decision support tool, and infographic are available on the AGA website (www.gastro.org).

Plans for Updating This Guideline

Guidelines need to be updated regularly to remain useful. This document will be updated when major new research is published. Keeping guidelines up to date is a challenging process. Future advances in technological platforms and models of guideline development incorporating living reviews and living guidelines will hopefully provide opportunities for more agile and rapid updates to recommendations and as new evidence emerges and as new interventions are studied, without duplication and reproduction of full guideline documents.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at http://dxdoi.org/10.1053/j.gastro.2022.04.017.

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Correspondence
Address correspondence to: Chair, Clinical Guidelines Committee, American Gastroenterological Association, National Office, 4930 Del Ray Avenue, Bethesda, Maryland 20814. e-mail: clinicalpractice@gastro.org.

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