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AGA SECTION

American Gastroenterological Association Institute Guideline on the Pharmacological Management of Irritable Bowel Syndrome

David S. Weinberg,[1] Walter Smalley,[2] Joel J. Heidelbaugh,[3] and Shahnaz Sultan[4,5]

[1]Fox Chase Cancer Center, Philadelphia, Pennsylvania; [2]VA Tennessee Valley Healthcare System, Vanderbilt University, Nashville, Tennessee; [3]University of Michigan Ann Arbor, Michigan; [4]Department of Veterans Affairs Medical Center, Gastroenterology Section, North Florida/South Georgia Veterans Health System, Division of Gastroenterology, Hepatology, and Nutrition, University of Florida, Gainesville, Florida; and [5]Minneapolis Veterans Affairs Health System, University of Minnesota, Minneapolis, Minnesota

This document presents the official recommendations of the American Gastroenterological Association (AGA) on the use of pharmacological agents for the treatment of irritable bowel syndrome (IBS) in adults. The guideline was developed by the Clinical Practice and Quality Measures Committee (currently the Clinical Practice Guideline Committee) and approved by the AGA Governing Board.

The guideline was developed using a process outlined elsewhere.[1] Briefly, the AGA process for developing clinical practice guidelines incorporates Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology[2] and best practices as outlined by the Institute of Medicine.[3] GRADE methodology was used to prepare the background information for the guideline and the technical review that accompanies it (Table 1).[4] Optimal understanding of this guideline will be enhanced by reading applicable portions of the technical review.

Members of the guideline panel, along with AGA support staff and a patient/consumer representative, met in person with the authors of the technical review on April 11, 2014. The information in the technical review was discussed in a systematic manner, facilitating subsequent creation of the guideline recommendations for or against each intervention. The strength of each recommendation was also rated as either strong or conditional.[1]

IBS is complex and encompasses several subgroups, including patients with constipation-predominant symptoms (IBS-C) and those with diarrhea-predominant symptoms (IBS-D). Many of the pharmacotherapy recommendations outlined in the following text apply to only one of these subgroups. The recommendations in this report apply to patients who meet the diagnostic criteria for IBS (IBS-C, IBS-D) and do not apply to the use of these agents for other symptoms or conditions. Use of nonpharmaceutical agents (fiber) and other interventions (dietary modification, biofeedback, acupuncture) used in the treatment of patients with IBS are not covered here.

1. Should Linaclotide Be Used in Patients With IBS-C?

The pooled effect estimates of 2 randomized controlled trials (RCTs) of linaclotide in patients with IBS-C showed a modest beneficial effect with a combined improvement in abdominal pain and an increase in the number of complete spontaneous bowel movements (Food and Drug Administration [FDA] response). Additionally, these 2 RCTs (plus another phase 2b trial) showed an improvement in global symptoms of IBS. Diarrhea leading to treatment discontinuation occurred in a small percentage of treated patients. This recommendation was made without taking resource use into account.

The AGA recommends using linaclotide (over no drug treatment) in patients with IBS-C. ***(Strong recommendation; High-quality evidence)***

Comments: ***Patients who place a high value on avoiding diarrhea and avoiding higher out-of-pocket expenses associated with linaclotide may prefer alternate treatments.***

2. Should Lubiprostone Be Used in Patients With IBS-C?

There are 2 randomized controlled trials of 12-week duration examining the effectiveness of lubiprostone for global symptom relief in patients with IBS-C, with a pooled effect estimate showing a small improvement in global symptoms of IBS. There were few adverse effects from using lubiprostone.

The AGA suggests using lubiprostone (over no drug treatment) in patients with IBS-C. ***(Conditional recommendation; Moderate-quality evidence)***

Comments: ***Patients who place a high value on avoiding higher out-of-pocket expenses associated with lubiprostone may prefer alternate treatments.***

Abbreviations used in this paper: AGA, American Gastroenterological Association; FDA, Food and Drug Administration; GRADE, Grading of Recommendations Assessment, Development and Evaluation; IBS, irritable bowel syndrome; IBS-C, irritable bowel syndrome with constipation; IBS-D, irritable bowel syndrome with diarrhea; RCT, randomized controlled trial.

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Table 1. GRADE Quality of Evidence, Strength of Recommendations, and Implications

Implications of strong and conditional (weak) guideline recommendations
- Strong recommendations
  - Patients: Most people in this situation would want the recommended course of action, and only a small proportion would not. Formal decision aids are not likely to be needed to help patients make decisions consistent with their values and preferences.
  - Clinicians: Most patients should receive the recommended course of action. Adherence to this recommendation according to guidelines could be used as a quality criterion or a performance indicator.
  - Policy makers: The recommendation can be adapted as a policy in most situations.
- Conditional (weak) recommendations
  - Patients: The majority of people in this situation would want the suggested course of action, but many would not. Decision aids are useful in helping patients make decisions consistent with their values and preferences.
  - Clinicians: Examine a summary of the evidence to help patients make a decision that is consistent with their own values and preferences (shared decision making).
  - Policy makers: There is a need for substantial debate and involvement of stakeholders.

NOTE. Reprinted with permission from Sultan et al.[2]

3. Should PEG Laxatives Be Used in Patients With IBS-C?

There are several trials examining the use of PEG laxatives in patients with chronic constipation; however, there is only one RCT evaluating the use of PEG solution for treating patients with IBS-C. This 4-week trial did not show a beneficial effect of PEG laxatives on IBS-related global symptom relief. However, these results should be interpreted with caution due to sparse data, methodological issues, and short follow-up. A large body of indirect evidence (showing efficacy of PEG laxatives for chronic constipation and for bowel lavage before colonoscopy) shows that laxatives are effective in increasing the frequency of bowel movements. Therefore, PEG laxatives may be useful in patients with IBS-C for specific symptom relief or as adjunctive treatment. Notably, there are few reported adverse effects and the cost is very low.

The AGA suggests using laxatives (over no drug treatment) in patients with IBS-C. ***(Conditional recommendation; Low-quality evidence)***

4. Should Rifaximin Be Used in Patients With IBS-D?

Pooled data from 2 RCTs showed a small but beneficial effect based on the combination of improvement in abdominal pain plus improvement in stool consistency (FDA response) in patients treated with rifaximin. Three RCTs demonstrated an improvement in IBS-related global symptoms. Additionally, these studies showed small improvements in abdominal pain and bloating, although these were of uncertain clinical significance. It is important to note that patients were treated for 2 weeks only and there is no evidence to support repetitive treatment. Although side effects were minimal, the cost of treatment for many patients may be quite high. At present, rifaximin is not approved by the FDA for the treatment of IBS-D.

The AGA suggests using rifaximin (over no drug treatment) in patients with IBS–D. ***(Conditional recommendation; Moderate-quality evidence)***

5. Should Alosetron Be Used in Patients With IBS-D?

Based on pooled data from multiple RCTs, patients treated with alosetron had improvement in abdominal pain and IBS-related global symptoms. Also, postmarketing data from an observational study suggested only rare occurrences of harm. The overall quality of the evidence was moderate (due to downgrading for inconsistency). When limited to consideration of abdominal pain improvement as the primary outcome, the quality of the evidence is greater (high). Several important caveats should be noted; alosetron is only FDA approved for use in women, and because of concerns about idiopathic, non–dose-dependent ischemic colitis (approximately 1 case/1000 patient-years), the drug was voluntarily withdrawn from the market and subsequently reintroduced only under a specific physician-based risk management program.

The AGA suggests using alosetron (over no drug treatment) in patients with IBS-D to improve global symptoms. ***(Conditional recommendation; Moderate evidence)***

6. Should Loperamide Be Used in Patients With IBS-D?

Available data investigating the use of loperamide specifically for the treatment of patients with IBS-D, as opposed to symptomatic relief of diarrhea for other disease states, is very limited. Two older RCTs that in the aggregate enrolled 42 patients failed to show a significant benefit in global relief of IBS-related symptoms. However, the quality of evidence from these trials was deemed very low due to methodological concerns and sparse data. There is, however, a large body of indirect evidence from a variety of other settings that shows the efficacy of loperamide in reducing stool frequency. Therefore, because of low cost, wide availability, and minimal adverse effects, loperamide can be viewed as a useful adjunct to other IBS-D therapies.

The AGA suggests using loperamide (over no drug treatment) in patients with IBS-D. ***(Conditional recommendation; Very low-quality evidence)***

7. Should Tricyclic Antidepressants Be Used in Patients With IBS?

A systematic review of multiple RCTs of 6- to 12-week duration showed a modest improvement in global relief and abdominal pain in patients treated with tricyclic antidepressants, although the overall body of evidence was low quality. Tricyclic antidepressants are a low-cost option for treatment of symptoms in patients with IBS; however, they should be used with caution in patients at risk for prolongation of the QT interval. In some patients, mild sedation may be a beneficial effect.

The AGA suggests using tricyclic antidepressants (over no drug treatment) in patients with IBS. *(Conditional recommendation; Low-quality evidence)*

8. Should Selective Serotonin Reuptake Inhibitors Be Used in Patients With IBS?

Pooled estimates from 5 RCTs of 6- to 12-week duration showed no improvement in global relief symptoms. Also, 4 RCTs of 6- to 12-week duration showed no improvement in abdominal pain. The risk of important adverse effects is minimal.

The AGA suggests against using selective serotonin reuptake inhibitors for patients with IBS. *(Conditional recommendation; Low-quality evidence)*

9. Should Antispasmodics Be Used in Patients With IBS?

A meta-analysis of 22 RCTs showed significant improvement in IBS-related global symptoms. Studies also showed modest improvement in abdominal pain symptoms with minimal risk of important adverse effects. The overall quality of evidence was low due to methodological limitations, heterogeneity, and publication bias. Notably, the reported data were based on continuous use, not as needed use, and not all antispasmodics studied are currently available in the United States.

The AGA suggests using antispasmodics (over no drug treatment) in patients with IBS. *(Conditional recommendation; Low-quality evidence)*

Summary

IBS is the most common diagnosis in clinical gastroenterology. It is estimated that approximately 10% to 15% of the general adult population is affected. Using the GRADE framework, this guideline offers 9 recommendations about pharmacological therapy for IBS-C and IBS-D. For this review, the important role of nonpharmacological therapies, including dietary and lifestyle modification, was not considered.

Despite the large number of published studies, in most cases our recommendations are weak because either (1) the quality of the available data and/or (2) the balance of risks and benefits for a particular therapy do not overwhelmingly support its use. In one case, alosetron for IBS-D, our recommendation is conditional, reflecting additional limitations based on FDA requirements. Given the growing focus on the need to show the comparative effectiveness of therapeutic alternatives, it is important to note that essentially no studies exist in this area comparing commonly used therapies with each other. Further, there are no substantial data comparing combinations of various therapies with placebo or with each other. Because no IBS therapy is uniformly effective, many patients describe a history of a variety of treatments alone or in combination. The present guideline is unable to address this important and frequent challenge of clinical care.

Recognizing these and other limitations, the recommendations included here represent a rigorous, evidence-based summary of extensive literature describing pharmacological therapy for IBS. Review of this guideline plus the associated technical review hopefully will promote effective shared decision making with patients for this common, chronic set of symptoms.

References

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Reprint requests
Address requests for reprints to: Chair, Clinical Practice and Quality Management Committee, AGA National Office, 4930 Del Ray Avenue, Bethesda, Maryland 20814. e-mail: msiedler@gastro.org; telephone: (301) 941-2618.

Acknowledgments
The Clinical Guidelines Committee included Steven L. Flamm (Northwestern Feinberg School of Medicine, Chicago, IL), Lauren Gerson (California Pacific Medical Center, San Francisco, CA), Ikuo Hirano (Northwestern University School of Medicine, Chicago, IL), Joseph K. Lim (Yale Liver Center, Yale University School of Medicine, New Haven, CT), Geoffrey C. Nguyen (Mount Sinai Hospital Centre for Inflammatory Bowel Disease, University of Toronto, Toronto, Ontario, Canada), Joel H. Rubenstein (Veterans Affairs Center for Clinical Management Research and Division of Gastroenterology, University of Michigan Medical School, Ann Arbor, MI), Siddharth Singh (Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester, MN), Neil Stollman (University of California San Francisco, Northern California Gastroenterology Consultants, San Francisco, CA), Santhi S. Vege (Pancreas Group, Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester, MN), and Yu-Xiao Yang (Division of Gastroenterology, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA).

Conflicts of interest
All members were required to complete a disclosure statement. These statements are maintained at the American Gastroenterological Association Institute headquarters in Bethesda, Maryland, and pertinent disclosures are published with the report. Dr Stollman has received research support from Furiex Pharmaceuticals for a study involving an investigational drug for IBS-D.