American Gastroenterological Association Institute Guideline on the Use of Pharmacological Therapies in the Treatment of Irritable Bowel Syndrome

David S. Weinberg,1 Walter Smalley,2 Joel J Heidelbaugh,3 Shahnaz Sultan,4 and the Clinical Guidelines Committee of the American Gastroenterological Association

1 Fox Chase Cancer Center, Philadelphia, PA; 2 VA Tennessee Valley Healthcare System; Vanderbilt University, Nashville, TN; 3 University of Michigan, Ann Arbor, MI; 4 Gastroenterology Section, Department of Veterans Affairs Medical Center, North Florida/South Georgia Veterans Health System; Division of Gastroenterology, Hepatology, and Nutrition, University of Florida, Gainesville, FL.

Acknowledgements: 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, Connecticut; Geoffrey Nguyen, Mount Sinai Hospital, New York, NY; Joel H. Rubenstein, Veterans Affairs Center for Clinical Management Research, Ann Arbor, Michigan and Division of Gastroenterology, University of Michigan Medical School, Ann Arbor, Michigan; 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; Yu-Xiao Yang, Division of Gastroenterology, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, Pennsylvania

Conflict of interest disclosure: All members were required to complete disclosure statement. These statements are maintained at the American Gastroenterological Association Institute (AGA) headquarters in Bethesda, Maryland and pertinent disclosure are published with the report. Dr. Stollman: Research support from FURIEX Pharmaceuticals for a study involving an investigational drug for IBS-D.
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). 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 utilizing a process outlined elsewhere. Briefly, the AGA process for developing clinical practice guidelines incorporates GRADE methodology and best practices as outlined by the Institute of Medicine.

GRADE methodology was utilized to prepare the background information for the guideline and the technical review which accompanies it. 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 12, 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

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2 Clinical Gastroenterology and Hepatology 2013;11:329–332
recommendation was also rated as either strong or conditional.  

Irritable bowel syndrome is complex and includes several subgroups including patients with constipation predominant symptoms (IBS-C) and those with diarrhea predominant symptoms (IBS-D).

Many of the pharmacotherapy recommendations outlined below apply to only one of these subgroups. The recommendations in this document apply to patients who meet the diagnostic criteria for IBS (C, D) and do not apply to the use of these agents for other symptoms or conditions. Use of non-pharmaceutical agents (fiber) and other interventions (biofeedback, acupuncture) used in the treatment of IBS are not covered here.

\[5\text{Table 1 in Clinical Gastroenterology and Hepatology 2013;11:329–332}\]
1. Should linaclotide be used in IBS-C patients?

The pooled effect estimates of two randomized controlled trials (RCTs) of linaclotide in IBS-C patients demonstrated a modest beneficial effect with a combined improvement in abdominal pain and an increase in the number of complete spontaneous bowel movements (FDA response). Additionally, these two RCTs (plus another phase IIb trial) showed an improvement in global IBS symptoms. Diarrhea leading to treatment discontinuation occurred in a small percentage of treated patients. Note that 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 will likely prefer alternate treatments.

2. Should lubiprostone be used in IBS-C patients?

There are two randomized controlled trials of 12 weeks 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 IBS symptoms. There were few side effects from using lubiprostone. More data on patient-important outcomes such as improvement in the number of SBM (spontaneous bowel movements) and abdominal pain are still needed.

The AGA suggests using lubiprostone (over no drug treatment) in IBS-C patients (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

3. Should PEG laxatives be used in IBS-C patients?

There are several trials examining the use of PEG laxatives in treating chronic constipation, however, there is only one RCT evaluating the use of PEG solution for treating IBS-C. This four-week trial did not demonstrate 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 prior to colonoscopy) demonstrates that laxatives are effective in increasing bowel movement frequency. Therefore, PEG laxatives may be useful in IBS-C patients for specific symptom relief or as adjunctive treatment. Notably, there are few reported side effects and the cost is very low.

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

4. Should rifaximin be used in IBS-D patients?

Pooled data from two RCTs demonstrated 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 demonstrated 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. While 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 an IBS-D indication.

### The AGA suggests using rifaximin (over no drug treatment) in IBS-D patients (Conditional recommendation, Moderate quality evidence)

**5. Should alosetron be used in IBS-D patients?**

Based on pooled data from multiple RCTs, patients treated with alosetron had improvement in abdominal pain and IBS-related global symptoms. Also, post-marketing data from an observational study suggested only rare occurrences of harm. The overall quality of the evidence was moderate (due to downgrading for imprecision). 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 IBS-D patients (Conditional recommendation, Moderate quality evidence)

**6. Should loperamide be used in IBS-D patients?**

Available data investigating the use of loperamide specifically for IBS-D, as opposed to symptomatic relief of diarrhea for other disease states, is very limited. Two older RCTs which in the aggregate
enrolled 42 patients failed to demonstrate 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 demonstrates the efficacy of loperamide in reducing stool frequency. Therefore, loperamide because of low cost, wide availability and minimal side effects can be viewed as a useful adjunct to other IBS-D therapies.

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

7. Should tricyclic antidepressants be used in IBS patients?

A systematic review of multiple RCTs of 6- to 12-week duration demonstrated a modest improvement in global relief and abdominal pain in patients treated with tricyclic antidepressants, though 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 IBS patients (Conditional recommendation; Low quality evidence)
8. Should selective serotonin reuptake inhibitors (SSRIs) be used in IBS patients?

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

The AGA suggests against using SSRIs for IBS patients (Conditional recommendation; Low quality evidence)

9. Should antispasmodics be used in IBS patients?

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

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

Summary

Irritable Bowel Syndrome is the most common diagnosis in clinical gastroenterology. It is estimated that approximately 10%-15% of general adult population is affected. Using the GRADE framework, this guideline offers 9 recommendations about pharmacological therapy for IBS-C and IBS-D.
Despite the large number of published studies, in most cases our recommendations are weak
because either the (1) 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 a conditional one reflecting additional limitations based on FDA requirements. It
is important to note that essentially no studies exist in this area comparing commonly employed
therapies to each other rather than to placebo, nor are there substantial data comparing
combinations of various therapies to placebo or to each other. As 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,
evidenced based summary of extensive literature describing pharmacologic 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 complaints.