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

Lin Chang,[1] Anthony Lembo,[2] and Shahnaz Sultan[3,4]

[1]Division of Digestive Diseases, David Geffen School of Medicine University of California, Los Angeles, Los Angeles, California; [2]Harvard Medical School, Beth Israel Deaconess, Boston, Massachusetts; [3]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 [4]Minneapolis Veterans Affairs Health System, University of Minnesota, Minneapolis, Minnesota

Irritable bowel syndrome (IBS) is a chronic functional gastrointestinal disorder characterized by abdominal pain and/or discomfort associated with altered defecation.[1] Other common symptoms include bloating, straining, rectal urgency, and the sensation of incomplete evacuation. These symptoms occur in approximately 11% of the world's population.[2–4] Women report symptoms of IBS more frequently than men; likewise, younger people are more susceptible than older people. IBS negatively impacts health-related quality of life[5] and results in a significant financial burden through reduced work productivity and increased use of health-related resources.[6]

The diagnosis of IBS is based on the presence of symptoms and, when clinically appropriate, exclusion of organic disease. In the absence of alarm symptoms (eg, rectal bleeding, unintentional weight loss, family history of colon cancer), diagnostic testing does not increase the sensitivity of the diagnosis.[7,8] The current Rome III criteria for IBS require the presence of recurrent abdominal pain and/or discomfort at least 3 days per month in the past 3 months that is associated with 2 or more of the following: improvement with defecation, onset associated with a change in frequency of stool, or onset associated with a change in form (appearance) of stool. Further subclassification is based on the predominant stool consistency: IBS with constipation (IBS-C), IBS with diarrhea (IBS-D), IBS with mixed pattern (IBS-M), and unsubtyped IBS.[1] Symptoms have to be present for at least 6 months. Current pharmacological treatments are generally aimed at improving one or more of the predominant symptoms, such as abdominal pain, constipation, or diarrhea. There is a lack of treatment data on IBS-M alone.

In this technical review, the American Gastroenterological Association (AGA) reviews commonly used pharmacological therapies for IBS. Selecting appropriate therapy for patients with IBS is a common clinical dilemma, particularly in a heterogeneous patient population with a range of symptoms. This review provides evidence-based information to guide clinicians and patients to the most appropriate therapy. However, the list of therapies in this review is not exhaustive and does not include nonpharmacological and alternative therapies. In this technical review, the GRADE (Grading of Recommendations Assessment, Development and Evaluation) system was used to assess the quality of evidence for the most commonly used pharmacological therapies for IBS.[9–11] GRADE has been adopted by several national and international societies, including the AGA, and is becoming the common methodology for the streamlined development of clear, transparent, and actionable guidelines.[9,11]

Methods

Overview

This technical review was conducted to inform the AGA guidelines for the management of IBS. Methods for deriving focused clinical questions, systematically reviewing and rating the quality of evidence for each outcome, and rating the overall quality of evidence were based on the GRADE framework, which has been described in more detail previously.[12–26] Using the PICO format, which frames a clinical question by defining a specific patient population (P), intervention (I), comparator (C), and outcome(s), we outlined a total of 9 questions (see Table 1).

Types of Participants, Interventions, and Comparators

We included studies of adults (18 years of age and older) with IBS using symptom-based diagnostic criteria. The interventions were linaclotide, lubiprostone, polyethylene glycol (PEG) laxative, rifaximin, alosetron, loperamide, tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), and antispasmodics. The comparators were placebos. It should be noted that there is a lack of comparative effectiveness studies in IBS.

Table 1. PICO Questions

Population(s)	Intervention(s)	Comparator	Outcome(s)

Adults with IBS-C	Linaclotide	Placebo or control	Beneficial
			  1. Symptom relief (FDA responder)
			  2. Global relief
			  3. Abdominal pain
			  4. CSBM or SBM
			  5. IBS-QOL
			Harms
			  6. Diarrhea leading to treatment discontinuation

Adults with IBS-C	Lubiprostone	Placebo or control	Beneficial
			  1. Symptom relief (FDA responder)
			  2. Global relief
			  3. Abdominal pain
			  4. CSBM or SBM
			  5. IBS-QOL
			Harms
			  6. Diarrhea leading to treatment discontinuation

Adults with IBS	Rifaximin	Placebo or control	Beneficial
			  1. Symptom relief (FDA responder)
			  2. Global relief
			  3. Abdominal pain
			  4. Bloating
			  5. IBS-QOL
			Harms
			  6. Adverse effects leading to treatment discontinuation

Adults with IBS	Alosetron	Placebo or control	Beneficial
			  1. Global relief
			  2. Abdominal pain
			  3. Urgency
			  4. Stool consistency
			  5. IBS-QOL
			Harms
			  6. Ischemic colitis
			  7. Serious complications of constipation

Adults with IBS	TCAs	Placebo or control	Beneficial
			  1. Global relief
			  2. Abdominal pain
			Harms
			  3. Anticholinergic effects

Adults with IBS	SSRIs	Placebo or control	Beneficial
			  1. Global relief
			  2. Abdominal pain
			Harms
			  3. Sexual dysfunction

Adults with IBS	Antispasmodics	Placebo or control	Beneficial
			  1. Global relief
			  2. Abdominal pain
			Harms
			  3. Adverse effects leading to treatment discontinuation

Adults with IBS	PEG laxatives	Placebo or control	Beneficial
			  1. Symptom relief (FDA responder)
			  2. Global relief
			  3. Abdominal pain
			  4. CSBM or SBM
			  5. IBS-QOL
			Harms
			  6. Diarrhea

Adults with IBS-C	Linaclotide	Lubiprostone	No studies

Outcomes of Interest

Using the GRADE approach to specify and prioritize patient-important outcomes, each outcome was ranked as critical, important, or not important for decision making. Only critical and important outcomes were summarized in the evidence profiles (Tables 2–10).

The Food and Drug Administration (FDA) responder outcome, when available, was considered a critical outcome. For IBS-C, the FDA defined a responder to be a participant who reported both a ≥30% reduction in average daily worst abdominal pain scores and an increase of ≥1 complete spontaneous bowel movement (CSBM) per week when compared with baseline for ≥6 of 12 weeks. For IBS-D, the FDA defined a responder to be a participant who reported both a ≥30% reduction in average daily worst abdominal pain scores and a ≥50% reduction in number of days per week with at least one stool that has a consistency of type 6 or 7 according to the Bristol Stool Form Scale[27] compared with baseline.[28] Adequate global relief was considered a critical efficacy outcome when the FDA responder end point was not available (the FDA responder definition was introduced in 2012). Important outcomes included abdominal pain response, CSBM response, improvement in IBS quality of life (QOL), improvement in stool consistency, and urgency. Although bloating is a prevalent symptom in patients with IBS, it was not specifically assessed because it is usually not a primary symptom end point and is often not adequately assessed in clinical trials. Harm outcomes included diarrhea requiring withdrawal from treatment, ischemic colitis, serious complications of constipation, or adverse effects leading to treatment discontinuation. Interventions were analyzed based on their ability to reduce an undesirable outcome (eg, failure of adequate relief response).

The minimal clinically important difference (often referred to as the smallest difference that clinicians and patients care about) is useful for decision making, because it represents the threshold for a clinically meaningful improvement for an individual patient. However, the difficulty in setting this threshold lies in the challenge of assigning an objective threshold to a subjective metric. For pharmacological treatments of IBS, the minimal clinically important threshold was defined as ≥10% by the authors. This was based on previous data measuring the minimal clinically important difference[29] as well as expert clinical opinion.

Information Sources and Study Selection

An information specialist, with input from the authors, developed and conducted several literature searches. The following bibliographic databases were searched through the OVID interface: MEDLINE, MEDLINE In-Process & Other Non-Indexed Citations, and EMBASE. Parallel searches included the Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Methodology Register, and Health Technology Assessment Database. The search strategy comprised controlled vocabulary, including the National Library of Medicine's Medical Subject Headings and keywords. The main search concepts included and combined were "irritable bowel syndrome" and "linaclotide" and "lubiprostone" and "polyethylene glycol" and "rifaximin" and "alosetron" and "tricyclic antidepressants" and "selective serotonin reuptake inhibitors" and "antispasmodics." Methodological

filters were applied to limit retrieval to randomized controlled trials (RCTs), meta-analyses, systematic reviews, and health technology assessments. The results were limited to English, human, and 1995 onward (see Supplementary Methods for detailed search strategies). An additional search was conducted using the aforementioned Medical Subject Headings and keywords and was limited to meta-analysis and technology assessments from 2004 onward.

In selecting studies, we followed the umbrella systematic review approach in which we identified published systematic reviews that fit predetermined eligibility criteria and were of high methodological rigor.[30] A systematic review was eligible for inclusion if it was recently conducted (search strategy executed within the past 10 years), evaluated the aforementioned outcomes of interest (outcomes important to patients), and provided a quantitative estimate of effect. We supplemented this by reviewing additional RCTs not included in the systematic reviews as well as references of relevant articles from the systematic reviews. When systematic reviews were not up to date or were incomplete, we performed our own meta-analysis (random effects model for 3 or more studies and fixed effects model for 2 studies) using the Cochrane Collaboration's RevMan 5.1 software.[31]

Evaluating the Evidence: Risk of Bias and Study Quality Appraisal

Within the GRADE framework, RCTs start as high-quality evidence but can be rated down for 5 possible reasons. Using GRADE, the quality of evidence for each outcome was evaluated for the following domains: risk of bias, inconsistency, indirectness, imprecision, and publication bias (see Glossary of Terms in Supplementary Methods). When the systematic reviews did not provide sufficient information to judge the quality of the evidence, individual studies were retrieved. Evidence ratings and qualitative judgments were determined via telephone discussion and consensus. For each question, an overall judgment of quality of evidence was made for a body of evidence that encompassed all critical outcomes.

Synthesis of Results and Summary Measures

When available, quantitative estimates of effect were applied from existing systematic reviews. Additional data were extracted and synthesized for some outcomes using RevMan.[31] If results were incomplete or unclear, study authors or study sponsors were contacted for additional information. Evidence profiles (Tables 2–10) were used to display the summary estimates as well as the body of evidence for each clinical question.

Question: Should Linaclotide Be Used in Patients With IBS-C?

Results

Linaclotide is a minimally absorbed guanylate cyclase C agonist that induces intestinal chloride and bicarbonate secretion via activation of the cystic fibrosis transmembrane conductance regulator (CFTR), resulting in acceleration of intestinal transit.[32,33] Activation of guanylate cyclase C by linaclotide also results in inhibition of colonic nociceptors in animal models.[34] Linaclotide is approved for the treatment

Table 2. Question: Should Linaclotide Be Used in Patients With IBS-C?

No. of participants (no. of studies), authors, follow-up	Quality assessment						Summary of findings				
							Study event rates (%)			Anticipated absolute effects	
	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	With placebo	With linaclotide	Relative effect (95% CI)	Risk with placebo	Risk difference with linaclotide (95% CI)
Failure of symptom relief (FDA responder) (critical outcome; assessed with patient diary)											
1604 (2 studies), Chey et al,[36] Rao et al,[37] 12 wk	No serious risk of bias	No serious inconsistency[a]	No serious indirectness	No serious imprecision	Undetected	⊕⊕⊕⊕ High	659/798 (82.6)	535/806 (66.4)	RR, 0.80 (0.76–0.85)	826 per 1000	165 fewer per 1000 (from 124 fewer to 198 fewer)
Failure of adequate global relief response (critical outcome; assessed with patient diary)											
1773 (3 studies), Chey et al,[36] Rao et al,[37] Johnston et al,[38] 12 wk	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	⊕⊕⊕⊕ High	709/883 (80.3)	530/890 (59.6)	RR, 0.73 (0.65–0.82)	803 per 1000	217 fewer per 1000 (from 145 fewer to 281 fewer)
Failure of adequate abdominal pain response (important outcome; assessed with patient diary)											
1604 (2 studies), Chey et al,[36] Rao et al,[37] 12 wk	No serious risk of bias	Serious inconsistency[b]	No serious indirectness	No serious imprecision	Undetected	⊕⊕⊕⊖ Moderate[b] due to inconsistency	612/798 (76.7)	511/806 (63.4)	RR, 0.83 (0.77–0.88)	767 per 1000	130 fewer per 1000 (from 92 fewer to 176 fewer)
Failure of adequate CSBM response (important outcome; assessed with patient diary)											
1775 (3 studies), Chey et al,[36] Rao et al,[37] Johnston et al,[38] 12 wk	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	⊕⊕⊕⊕ High	830/885 (93.8)	712/890 (80)	RR, 0.86 (0.83–0.89)	938 per 1000	131 fewer per 1000 (from 103 fewer to 159 fewer)
Failure to achieve clinically meaningful improvement in IBS-QOL (important outcome; assessed with IBS-QOL[c])											
1659, (2 studies), Chey et al,[36] Rao et al,[37] 12 wk	No serious risk of bias	Serious inconsistency[d]	No serious indirectness	No serious imprecision	Undetected	⊕⊕⊕⊖ Moderate[d] due to inconsistency	506/827 (61.2)	399/832 (48)	RR, 0.78 (0.72–0.86)	612 per 1000	135 fewer per 1000 (from 86 fewer to 171 fewer)
Adverse events (diarrhea) leading to treatment discontinuation (important outcome)											
1773 (3 studies), Chey et al,[36] Rao et al,[37] Johnston et al,[38] 12 wk	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	⊕⊕⊕⊕ High	2/883 (0.23)	42/890 (4.7)	RR, 14.8 (4–54)	2 per 1000	31 more per 1000 (from 7 more to 120 more)

[a]The I^2 was >50%, but we did not rate down due to overlapping 95% CI.
[b]We rated down for inconsistency due to an I^2 of 85%.
[c]A clinically meaningful improvement was defined as an increase in IBS-QOL of ≥14 points.
[d]We rated down for inconsistency due to an I^2 of 78%.

of adult men and women with IBS-C at a dosage of 290 μg daily and chronic idiopathic constipation at a dosage of 145 μg daily in North America, United Kingdom, and some countries in Europe.

Three RCTs including 1773 patients (linaclotide, n = 890; placebo, n = 883) compared linaclotide with placebo for the treatment of patients with IBS-C.[35–38] All were blinded and achieved allocation concealment. The patient populations were similar in the 2 phase 3 RCTs but differed slightly from those in the phase 2b RCT. All patients met Rome II diagnostic criteria for IBS and had <3 spontaneous bowel movements (SBMs) per week and one or more of the following symptoms with ≥25% of bowel movements for at least 12 weeks in the 12 months before study entry: straining, lumpy or hard stools, or sensation of incomplete evacuation. During the pretreatment baseline period, patients were required to have an average daily worst abdominal pain score of ≥3 on a 11-point numeric rating scale (0 = no abdominal pain, 10 = severe abdominal pain), an average of <3 CSBMs per week, and ≤5 SBMs per week to be eligible for randomization in the 2 phase 3 RCTs. In the phase 2b RCT, patients were required to report an average daily abdominal pain or discomfort score of ≥2 on a 5-point scale (1 = none, 5 = very severe), <3 CSBMs per week, and ≤6 SBMs per week during the baseline period. The phase 3 RCTs assessed the efficacy of linaclotide at a dosage of 290 μg/day, whereas the phase 2b RCT was a dose-ranging study with linaclotide at dosages of 75, 150, 300, or 600 μg/day.

The 2 phase 3 RCTs (1604 patients; linaclotide, n = 806; placebo, n = 798) assessed symptom relief using the FDA responder definition for IBS-C. Compared with placebo, linaclotide showed a significantly lower failure rate of symptom relief using the FDA definition of a responder (relative risk [RR], 0.8; 95% confidence interval [CI], 0.76–0.85). Based on a placebo failure rate of 82.6%, use of linaclotide would result in 165 fewer failures per 1000 (95% CI, 124 fewer to 198 fewer). All 3 studies used a global assessment measuring adequate relief of symptoms of IBS-C. Compared with placebo, linaclotide showed a lower failure rate (RR, 0.73; 95% CI, 0.65–0.82). Based on a placebo failure rate of 80.3%, use of linaclotide would result in 217 fewer failures per 1000 (95% CI, 145 fewer to 281 fewer).

With respect to individual symptoms, all studies evaluated failure of adequate abdominal pain response. Compared with placebo, linaclotide showed a lower failure rate of adequate abdominal pain response (RR, 0.83; 95% CI, 0.77–0.88). Based on a placebo failure rate of 76.7%, use of linaclotide would result in 130 fewer failures per 1000 (95% CI, 92 fewer to 176 fewer). Two of the 3 studies also measured failure of adequate CSBM response. Linaclotide had a lower failure rate compared with placebo (RR, 0.86; 95% CI, 0.83–0.89). Based on a placebo failure rate of 93.8%, use of linaclotide would result in 131 fewer failures per 1000 (95% CI, 103 fewer to 159 fewer).

Failure to achieve a clinically meaningful improvement in IBS-QOL[39] was measured in the 3 studies. Compared with placebo, linaclotide showed a lower failure rate (RR, 0.78; 95% CI, 0.72–0.86). Based on a placebo failure rate of 61.2%, use of linaclotide would result in 135 fewer IBS-QOL failures per 1000 (95% CI, 86 fewer to 171 fewer).

With regard to diarrhea leading to treatment withdrawal, linaclotide was associated with a higher number of diarrhea events (RR, 14.8; 95% CI, 4–54). Based on a placebo incidence of 2 diarrhea events leading to treatment withdrawal per 1000, use of linaclotide would result in 31 more diarrhea events per 1000 (95% CI, 7 more to 120 more).

> **The overall quality of evidence across all critical outcomes for linaclotide was high.**

Discussion

Three multicenter, placebo-controlled RCTs supported the efficacy of linaclotide in the global improvement of symptoms of IBS. Our results are similar to those in a recently published meta-analysis by Videlock et al.[35] The two phase 3 trials by Chey et al[36] and Rao et al[37] are the only studies of IBS-C in which the primary outcome is the FDA responder end point for IBS-C.[28] A recent study showed that the FDA responder definition is clinically meaningful in patients with IBS-C with excellent specificity and reasonable sensitivity.[40] Likewise, using patient rating of change assessments, a greater proportion of patients taking linaclotide who were FDA responders reported that abdominal pain (93.4% vs 63.4%) and CSBM (92.3% vs 51.7%) were at least somewhat relieved compared with FDA nonresponders.[41] Although adequate relief of symptoms of IBS is no longer accepted by the FDA as a valid primary outcome measure in clinical trials of IBS, the efficacy of linaclotide versus placebo using the end point of adequate relief of symptoms of IBS was similar to that using the FDA responder definition, although the end point of adequate relief showed a slightly better RR. Based on the high quality of evidence for global assessment of symptoms of IBS, linaclotide has clinically meaningful beneficial effects compared with placebo.

Relief of abdominal pain has always been an important goal in the treatment of patients with IBS because pain is one of the main predictors of severity,[42,43] health-related QOL,[44] and physician visits.[45] Compared with placebo, a greater proportion of patients treated with linaclotide reported improvement in abdominal pain response. The 2 phase 3 trials found that the maximal effect of abdominal pain relief could take up to 12 weeks. Therefore, the beneficial effects on bowel habits may precede those on abdominal pain. Diarrhea was the most frequent treatment-related adverse event. Although most cases were mild to moderate in severity and only a small percentage (∼5%) of patients withdrew from the study because of diarrhea, it is a notable adverse effect to discuss with patients when considering the use of linaclotide.

Question: Should Lubiprostone Be Used in Patients With IBS-C?

Results

Lubiprostone is a chloride channel type 2 activator that increases chloride influx into the lumen of the

Table 3. Question: Should Lubiprostone Be Used in Patients With IBS-C?

No. of participants (no. of studies), author, follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With placebo	With lubiprostone		Risk with placebo	Risk difference with lubiprostone (95% CI)
Failure of symptom relief (FDA responder) (critical outcome)											
452 (2 RCTs), Drosssman et al,[47] 12 wk	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious imprecision[a]	Undetected	⊕⊕⊕⊖ Moderate[a] due to imprecision	138/163 (84.7)	213/289 (73.7)	RR, 0.88 (0.79–0.96)	847 per 1000	102 fewer per 1000 (from 34 fewer to 178 fewer)
Failure of adequate relief response (global response)[b] (critical outcome; assessed with weekly patient diary)											
1154 (2 RCTs[c]), Drosssman et al,[47] 12 wk	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious imprecision[a]	Undetected	⊕⊕⊕⊖ Moderate[a] due to imprecision	346/385 (89.9)	631/769 (82.1)	RR, 0.93 (0.87–0.96)	899 per 1000	63 fewer per 1000 (from 36 fewer to 117 fewer)
Failure of adequate abdominal pain response[d] (important outcome)											
452 (2 RCTs), Drosssman et al,[47] 12 wk	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious imprecision[a]	Undetected	⊕⊕⊕⊖ Moderate[a] due to imprecision	122/163 (74.8)	183/289 (63.3)	RR, 0.85 (0.76–0.95)	748 per 1000	112 fewer per 1000 (from 37 fewer to 180 fewer)
Failure of adequate SBM response[d,e] (important outcome)											
505 (2 RCTs), Drosssman et al,[47] 12 wk	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious imprecision[a]	Undetected	⊕⊕⊕⊖ Moderate[a] due to imprecision	99/180 (55.0)	160/325 (49.2)	RR, 0.90 (0.75–1.10)	550 per 1000	55 fewer per 1000 (from 138 fewer to 55 more)
Failure to achieve clinically meaningful improvement in IBS-QOL (important outcome) See text											
Adverse events leading to treatment discontinuation (important outcome)											
1166 (2 RCTs), Drosssman et al,[47] 12 wk	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious imprecision	Undetected	⊕⊕⊕⊖ Moderate due to imprecision	7/387 (1.8)	5/779 (0.6)	RR, 0.36 (0.11–1.12)	18 per 1000	615 more per 1000 (from 16 fewer to 2 more)

[a]The upper boundary of the CI did not cross our minimal clinically important threshold of at least 10%; therefore, we rated down for imprecision.
[b]Adequate relief response was based on the overall responder rate, which was defined as a monthly responder for at least 2 of 3 months. A monthly responder was defined as response of moderate relief or better for 4 of 4 weeks or response of significant relief.
[c]Two separate, identically designed, multicenter studies were analyzed and reported together in a single paper.
[d]Data for this outcome was provided by the company as a post-hoc analysis of a subgroup.
[e]SBM was used to inform this outcome (as well as FDA responder outcome) because CSBM data was not obtained in the study.

gastrointestinal tract, resulting in acceleration of intestinal transit.[46] Lubiprostone is approved in the United States, Japan, and a few countries in Europe for the treatment of adult women with IBS-C at a dosage of 8 μg twice daily and adult men and women with chronic constipation at a dosage of 24 μg twice daily. Dichotomous data were only available from 2 identically designed phase 3 RCTs.[47] These trials, which were analyzed and reported together in one paper,[47] included 1154 patients with IBS-C (lubiprostone, n = 769; placebo, n = 385). The dosage of lubiprostone assessed was 8 μg twice daily. Both studies achieved adequate blinding and allocation concealment. The patient populations were similar in the 2 phase 3 RCTs. All patients met Rome II diagnostic criteria for IBS-C and during the 4-week screening period reported a monthly average assessment of mild or greater severity of abdominal pain/discomfort and any 2 of the following: <3 SBMs per week for at least ≥25% of the time, at least 25% of SBMs with straining of moderate or greater severity, and 25% of SBMs with a stool consistency of hard or very hard stool. The primary efficacy end point was a responder for at least 2 out of 3 months of the study. A monthly responder was defined as a patient who reported either moderate or significant relief of their symptoms of IBS for all 4 weeks of the month or significant relief for at least 2 weeks of the month. These studies were conducted before the introduction of the FDA responder end point. Responder rates for global assessment and a modified FDA end point as well as abdominal pain and SBM frequency for 6 of 12 treatment weeks for each of the 2 studies were provided by the sponsor. Because these studies did not measure CSBMs, SBM response was assessed. In addition, a 5-point Likert scale for abdominal pain (0–4 scale, where 0 = mild and 4 = very severe) was used. Only patients with a mean weekly abdominal pain severity score at baseline of ≥1.36 on a 5-point scale (equivalent of the FDA-recommended baseline rating of ≥3 out of 10 on an 11-point scale) were included in our analysis.

Compared with placebo, lubiprostone showed a significantly lower failure rate of the primary end point (RR, 0.93; 95% CI, 0.87–0.96). Because the upper boundary of the CI crossed our minimal clinically important threshold of at least 10%, we rated down for imprecision. Based on a placebo failure rate of 89.8%, use of lubiprostone would result in 63 fewer failures per 1000 (95% CI, 36 fewer to 117 fewer). Compared with placebo, lubiprostone showed a significantly lower failure rate of the modified FDA response (RR, 0.88; 95% CI, 0.79–0.96). Based on a placebo failure rate of 84.7%, use of lubiprostone would result in 102 fewer failures per 1000 (95% CI, 34 fewer to 178 fewer).

Compared with placebo, lubiprostone showed a significantly lower failure rate of adequate abdominal pain response (RR, 0.85; 95% CI, 0.76–0.95). Based on a placebo failure rate of 74.8%, use of lubiprostone would result in 112 fewer failures per 1000 (95% CI, 37 fewer to 180 fewer). Compared with placebo, use of lubiprostone was not associated with a significantly lower failure rate of adequate SBM response (RR, 0.90, 95% CI, 0.75–1.10). Based on a placebo failure rate of 55%, use of lubiprostone would result in 55 fewer failures per 1000 (95% CI, 138 fewer to 55 more).

The quality of evidence for these 4 outcomes was rated down for imprecision. Other important outcomes could not be assessed based on the available data, including assessment of improvement in health-related QOL and diarrhea leading to treatment withdrawal. Adverse events related to the gastrointestinal tract were reported in 19% of patients receiving lubiprostone compared with 14% receiving placebo. A similar number of patients withdrew due to adverse events in the lubiprostone group (12.8%) vs placebo (12.3%).

> **The overall quality of evidence across all critical outcomes for lubiprostone was moderate.**

Discussion

The 2 multicenter placebo-controlled RCTs with dichotomous data to support the efficacy of lubiprostone 8 μg twice daily in patients with IBS-C were combined and reported in 2009.[47] Because these trials predate the FDA responder definition for IBS-C, the measurement and definitions of end points differ significantly from the linaclotide trials and did not include the FDA responder end point. However, a post-hoc analysis was performed on a modified FDA responder definition: adequate abdominal pain and SBM response. Although there was a significantly beneficial effect of lubiprostone on global outcomes and abdominal pain response compared with placebo, the differences did not meet the threshold for being clinically meaningful. However, only a subset of patients was included in this analysis based on baseline abdominal pain severity; therefore, this symptom end point may not have been adequately powered. Compared with placebo, lubiprostone was not associated with an adequate SBM response rate. It is not known if lubiprostone would be associated with a significantly lower failure of an adequate CSBM response because this was not measured.

Higher dosages of lubiprostone, such as 24 μg twice daily, currently recommended for chronic idiopathic constipation, were included in a phase 2b trial of IBS-C and showed greater relief in constipation-related end points (eg, severity of constipation, stool consistency, and SBM rate) with little additional benefit on abdominal pain/discomfort and at the expense of a higher incidence of adverse effects such as nausea and diarrhea compared with a dosage of 8 μg twice daily.[48] A recently reported long-term safety extension study in patients with IBS-C found lubiprostone to be safe and well tolerated for up to 13 months of treatment.[49]

Question: Should PEG Laxatives Be Used in Patients With IBS-C?

Results

PEG is a long-chain polymer of ethylene oxide, which acts as an osmotic laxative and is FDA approved for the short-term treatment of adults and children with occasional constipation. Only one PEG study, which was a placebo-

Table 4. Question: Should PEG Laxatives Be Used in Patients With IBS-C?

No. of participants (no. of studies), author, follow-up	Quality assessment						Summary of findings				
							Study event rates (%)			Anticipated absolute effects	
	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	With placebo	With PEG	Relative effect (95% CI)	Risk with placebo	Risk difference with PEG (95% CI)
Failure of symptom relief (FDA responder) (critical outcome; assessed with patient diary)											
122 (n, post-hoc analysis) (1 RCT), Chapman et al,[50] 4 wk	Serious risk of bias[a]	No serious inconsistency	No serious indirectness	Serious imprecision[b]	Undetected	⊕⊕⊖⊖ Low[a,b] due to risk of bias and imprecision	49/62 (79.0)	40/60 (66.7)	RR, 0.90 (0.66–1.2)	790 per 1000	79 fewer per 1000 (from 269 fewer to 158 more)
Failure of adequate relief response (important outcome): not reported											
Failure of adequate abdominal pain response (important outcome; assessed with patient diary)											
122 (n, intention to treat analysis) (1 RCT), Chapman et al,[50] 4 wk	Serious risk of bias[a]	No serious inconsistency	No serious indirectness	Serious imprecision[b]	Undetected	⊕⊕⊖⊖ Low[a,b] due to risk of bias and imprecision	37/62 (60.0)	32/60 (53.3)	RR, 0.93 (0.67–1.4)	600 per 1000	42 fewer per 1000 (from 197 fewer to 239 more)
Failure of adequate CSBM response (important outcome; assessed with patient diary): not reported											
Failure to achieve clinically meaningful improvement in IBS-QOL (important outcome; assessed with SF-36[c]): not reported											
Adverse effects leading to treatment discontinuation[d] (important outcome): not reported											

[a]A post-hoc modified intention-to-treat analysis was performed in this single-center industry-sponsored study with a very short duration of treatment. We excluded one other study (Khoshoo et al) because a different population (adolescents) and comparator (PEG plus tegaserod) were used.
[b]The CI was very wide due to the small sample size and few events in the study.
[c]The SF-36 instrument was used in the study, but raw data were not presented.
[d]Only 2 patients discontinued treatment due to adverse events. The study reported that 4.5% of patients in the PEG arm experienced abdominal pain (vs 3% in the placebo arm) and 4.5% experienced diarrhea (vs 4.3% in the placebo arm).

controlled trial, met the inclusion criteria. This study,[50] which was a 4-week placebo-controlled RCT, compared the efficacy of PEG 3350 in combination with sodium chloride, sodium bicarbonate, potassium chloride, sweetener (acesulfame potassium) and lemon-lime flavoring or placebo (13.8 sucrose with 0.1 g lemon and lime flavoring) (PEG+E; Movicol, Norgine, Uxbridge, UK), and placebo in 139 patients (n, intention to treat analysis) with IBS-C (PEG+E, n = 68; placebo, n = 71). Movicol is approved for the treatment of chronic constipation in children and adults in Europe as well as in other countries. PEG 3350 without electrolytes is widely available for the treatment of constipation, including in the US where it is available over-the-counter. Patients with IBS were eligible for enrollment if they met the Rome III criteria for IBS and the constipation subtype and reported <3 SBMs during the last 7 days of the run-in phase.[1] Sachets of 13.8 g PEG+E were provided to the patients. Two sachets were taken daily on the first 2 days and then patients were allowed to adjust their daily dose between 1 and 3 sachets based on stool consistency, with the aim of achieving a Bristol Stool Form Scale[27] score of types 3 to 5 (considered within normal range). All were blinded and likely achieved allocation concealment.

The primary end point was the mean number of SBMs per day in the last treatment week. However, a post-hoc analysis (of 122 patients) utilized a modified FDA end point for IBS-C by using SBMs rather than CSBMs.[28] Responders were defined as patients with pain reduction of >30%, >3 SBMs per week, and an increase of 1 SBM per week. Compared with placebo, PEG+E did not show a significantly lower failure rate of symptom relief using the modified FDA responder definition (RR, 0.9; 95% CI, 0.66–1.2). Based on a placebo failure rate of 79.0%, use of PEG+E would result in 79 fewer failures per 1000 (95% CI, 269 fewer to 158 more). For adequate relief of abdominal pain response (>30% reduction in pain in the last treatment week), PEG+E did not show a significantly lower failure rate compared with placebo (RR, 0.93; 95% CI, 0.67–1.4). Based on a placebo failure rate of 60%, use of PEG+E would result in 42 fewer failures per 1000 (95% CI, 197 fewer to 239 more). The important outcomes of CSBM responder rate, improvement in IBS-QOL, and withdrawal of treatment due to abdominal pain or diarrhea were not assessed based on the available data. Health-related QOL was measured using the generic QOL SF-36 questionnaire. However, there were no clinically meaningful differences in the SF-36 scores between PEG+E and placebo. Additional limitations of this study included that it was a single-center study with a relatively short duration of treatment for an IBS clinical trial[28] and used varying treatment doses per patient.

> **The overall quality of evidence across all critical outcomes for PEG laxatives was low.**

Discussion

In clinical practice, PEG is commonly used for chronic constipation and has been shown to be efficacious[51];

however, its effects on symptoms of IBS have not been well studied. Chapman et al[50] did not show a statistically significant or clinically meaningful improvement in abdominal pain or in the modified FDA responder end point for IBS-C in patients receiving PEG+E compared with placebo. Although this study showed a statistically significant improvement of CSBM frequency with PEG+E compared with placebo, the response rates could not be calculated based on the available data. Therefore, based on this study, PEG does not appear to improve abdominal pain in patients with IBS-C. There are insufficient data to confidently determine its effect on global symptoms. Although PEG has been shown to improve symptoms of constipation, larger high-quality studies are clearly needed to adequately evaluate the efficacy of PEG in patients with IBS-C in whom abdominal pain is a more predominant symptom.

Question: Should Rifaximin Be Used in Patients With IBS-D?

Results

Three RCTs including 1258 patients (rifaximin, n = 624; placebo, n = 634) compared rifaximin with placebo for the treatment of patients with nonconstipating IBS.[52–55] Two phase 3[53] studies evaluated the efficacy of rifaximin using a dosage of 550 mg 3 times a day for 2 weeks. The third study, which was a phase 2b trial, included multiple doses up to 4 weeks in duration, although the primary comparison was 550 mg twice daily for 14 days followed by 14 days of placebo.[55] All studies were blinded and likely achieved allocation concealment. All studies used Rome II diagnostic criteria. In the 2 phase 3 trials,[53] patients had to report that they did not have adequate relief of their IBS and IBS-related bloating, an average daily abdominal pain and bloating scores from 2 to 4.6 on a 7-point Likert scale (0–6) and an average daily stool consistency of ≥3.5 on a 5-point Likert scale (1 = very hard; 5 = watery). The majority of patients had IBS-D.

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 showed a lower failure rate of the FDA responder end point for IBS-D (RR, 0.85; 95% CI, 0.78–0.94). Based on a placebo failure rate of 82.0%, use of rifaximin would result in 94 fewer failures per 1000 (95% CI, 38 fewer to 138 fewer). Because the upper boundary of the CI crossed our minimal clinically important threshold of at least 10%, we rated down for imprecision for this outcome.

Improvement in global relief was evaluated in all 3 trials. Compared with placebo, rifaximin showed a lower failure rate of adequate global relief and discomfort (RR, 0.87; 95% CI, 0.80–0.94). Based on a placebo failure rate of 65.3%, use of rifaximin would result in 85 fewer failures per 1000 (95% CI, 39 fewer to 131 fewer). Again, because the CI crossed our minimal clinically important threshold of 10%, we rated down for imprecision for this outcome.

In the phase 3 trials, rifaximin showed a lower failure rate of adequate relief of bloating compared with placebo

Table 5. Question: Should Rifaximin Be Used in Patients With IBS-D?

	Quality assessment						Summary of findings				
							Study event rates (%)			Anticipated absolute effects	
No. of participants (no. of studies), authors, follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	With placebo	With rifaximin	Relative effect (95% CI)	Risk with placebo	Risk difference with rifaximin (95% CI)
Failure of symptom relief (FDA responder) (critical outcome; assessed with patient diary)											
1258 (2 RCTs),[a,b] Pimentel et al,[53] 12 wk	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious imprecision[c]	Undetected	⊕⊕⊕⊖ Moderate[c] due to imprecision	397/634 (62.6)	333/624 (53.4)	RR, 0.85 (0.78–0.94)	820 failures per 1000	94 fewer failures per 1000 (from 38 fewer to 138 fewer)
Failure of adequate global relief response (critical outcome; assessed with patient diary)											
1646 (3 RCTs), Lembo et al,[55] Pimentel et al,[53] 10–16 wk	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious imprecision[c]	Undetected	⊕⊕⊕⊖ Moderate[c] due to imprecision	543/831 (65.3)	461/815 (56.6)	RR, 0.87 (0.80–0.94)	653 per 1000	85 fewer per 1000 (from 39 fewer to 131 fewer)
Failure of adequate abdominal pain response[d] (important outcome; assessed with patient diary)											
1260 (2 RCTs), Pimentel et al,[53] 12 wk	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious imprecision[c]	Undetected	⊕⊕⊕⊖ Moderate[c] due to imprecision	410/634 (64.7)	352/624 (56.4)	RR, 0.87 (0.80–0.95)	647 per 1000	84 fewer per 1000 (from 32 fewer to 129 fewer)
Failure of adequate bloating response[e] (important outcome; assessed weekly with patient diary)											
1260 (2 RCTs), Pimentel et al,[53] 12 wk	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious imprecision[c]	Undetected	⊕⊕⊕⊖ Moderate[c] due to imprecision	442/634 (69.7)	373/624 (59.8)	RR, 0.86 (0.79–0.93)	697 per 1000	98 fewer per 1000 (from 49 fewer to 146 fewer)
Failure to achieve clinically meaningful improvement in IBS-QOL (important outcome): not reported											
Adverse effects leading to treatment discontinuation (important outcome)											
1260 (2 RCTs), Pimentel et al,[53] 12 wk	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious imprecision[c]	Undetected	⊕⊕⊕⊖ Moderate[c] due to imprecision	9/634 (1.4)	8/624 (1.3)	RR, 0.90 (0.35–2.33)	14 per 1000	1 fewer per 1000 from 9 fewer to 19 more)

[a]An additional study (Pimentel et al[56]) was not included because outcomes were measured as percent improvement in symptoms and did not include a responder outcome.
[b]Two identical phase 3 studies (TARGET 1 and TARGET 2) were published together in one report.
[c]The upper boundary of the CI did not cross our minimal clinically important difference of 10%; therefore, we rated down for imprecision.
[d]The adequate abdominal pain response outcome was based on the "daily IBS-related abdominal pain" measurement.
[e]The adequate bloating response was based on the "weekly IBS-related bloating" measurement.

(RR, 0.86; 95% CI, 0.79–0.93). Based on a placebo failure rate of 69.7%, rifaximin would result in 98 fewer failures per 1000 (95% CI, 49 fewer to 146 fewer). Again, because the CI crossed our minimal clinically important threshold of 10%, we rated down for imprecision for this outcome. Improvement in abdominal pain was evaluated in the 2 phase 3 trials. Compared with placebo, rifaximin showed a lower failure rate of relief of abdominal pain (RR, 0.87; 95% CI, 0.80–0.95). Based on a placebo failure rate of 64.7%, rifaximin would result in 84 fewer failures per 1000 (95% CI, 32 fewer to 129 fewer). Other important outcomes could not be assessed based on the available data, including assessment of SBM frequency, CSBM responder rate, improvement in health-related QOL, and diarrhea leading to treatment withdrawal.

> **The overall quality of evidence across all critical outcomes for rifaximin was moderate.**

Discussion

Three placebo-controlled RCTs with dichotomous end points support the efficacy of rifaximin in patients with IBS-D but, based on our threshold (of crossing the minimal clinically important difference), they failed to show clinically meaningful improvements across all key symptoms associated with IBS-D; the overall quality of rifaximin was rated as moderate. In contrast to other treatments for IBS, which were taken daily throughout the assessment period, rifaximin was administered for only 14 days. The primary and secondary end points were assessed during the 4 weeks after completion of treatment. In the phase 3 clinical trials, rifaximin 550 mg 3 times a day for 14 days was studied though 2 additional trials not included in this analysis that reported improvement in symptoms of IBS in all subtypes with 10 days of treatment with rifaximin at dosages of 400 mg 3 times a day[56] and 400 mg twice a day.[57]

A meta-analysis by Menees et al[54] also reported similar efficacy of rifaximin in improving global symptoms of IBS and bloating. In addition, they noted that studies with older patients and more women had higher response rates. The efficacy of rifaximin may diminish over time; therefore, repeated treatments may be necessary. The efficacy and safety of repeat treatment with rifaximin was recently shown to result in significant improvement as compared to placebo for IBS-related abdominal pain and stool consistency during the 4 week treatment-free follow-up period.[58]

Question: Should Alosetron Be Used in Patients With IBS-D?

Results

Alosetron is a selective 5-HT$_3$ antagonist, and its efficacy in nonconstipated IBS has been evaluated in multicenter RCTs. The mechanism of action is believed to be both centrally and peripherally mediated.[59] 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.[60]

Eight RCTs in 4227 patients (alosetron, n = 2517; placebo, n = 1710) compared the efficacy of alosetron with placebo in patients with nonconstipating IBS.[61–68] Seven of the 8 studies evaluated the efficacy of alosetron over a 12-week period, and the remaining study was a 48-week trial. All studies were blinded and likely achieved allocation concealment. Six studies[61–64,66,67] used Rome I diagnostic criteria, and 2 used Rome II criteria.[65,68] Most, if not all, patients had IBS-D except for one study[63] that enrolled a fairly equal distribution of patients with IBS-D, IBS alternating type, and IBS-C. Four of the studies[61,64–66] assessed the efficacy of alosetron only at a dosage of 1 mg twice daily, and 4 trials[61,63,67,68] were dose-ranging studies. Only dosages of 0.5 and 1 mg twice daily were included in this analysis.

Global assessment of symptoms of IBS was measured in only 2 of the RCTs (1506 patients; alosetron, n = 1061; placebo, n = 445). Both 12-week studies enrolled only female patients with IBS-D who met Rome II criteria and had relatively more severe disease. One RCT[68] was a dose-ranging study that assessed 3 different dosages of alosetron: 0.5 mg daily, 1 mg daily, and 1 mg twice daily. The second study[65] included only patients who had a lack of satisfactory control of bowel urgency on at least 50% of days. The dosage of alosetron was 1 mg twice daily. Both studies used a global improvement scale, which was a 7-point balanced Likert scale. A responder was defined as a patient who reported either moderately or substantially improved symptoms of IBS compared with the way they felt during the 3 months before entering the study. Compared with placebo, alosetron showed a significantly lower failure rate of global improvement (RR, 0.60; 95% CI, 0.54–0.67). Based on a placebo failure rate of 62.5%, use of alosetron would result in 250 fewer failures per 1000 (95% CI, 206 fewer to 287 fewer). The overall quality of evidence for global assessment was rated down due to inconsistency.

Seven studies evaluated the efficacy of alosetron in improving abdominal pain. Six studies measured adequate relief of IBS pain and discomfort,[61] and one assessed the proportion of patients who had at least 10% improvement in abdominal pain and discomfort using a visual analogue scale.[63] Compared with placebo, alosetron showed a lower failure rate of adequate relief of IBS pain and discomfort (RR, 0.83; 95% CI, 0.79–0.88). Based on a placebo failure rate of 65.1%, use of alosetron would result in 111 fewer failures per 1000 (95% CI, 78 fewer to 137 fewer). The quality of evidence for this outcome was high.

Responder definitions were not reported for urgency and stool consistency, and therefore these outcomes could not be adequately evaluated. However, in all of the individual studies, alosetron was shown to improve urgency and stool consistency.

The effect of alosetron on QOL was evaluated in a 12-week, placebo-controlled, dose-ranging (alosetron 0.5 mg daily, 1 mg daily, and 1 mg twice daily) RCT of 705 women

Table 6. Question: Should Alosetron Be Used in Patients With IBS-D?

No. of participants (no. of studies), authors, follow-up	Quality assessment						Summary of findings				
							Study event rates (%)			Anticipated absolute effects	
	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	With placebo	With alosetron	Relative effect (95% CI)	Risk with placebo	Risk difference with alosetron (95% CI)
Failure of adequate global relief response (critical outcome; assessed with patient diary)											
1506 (2 RCTs), Lembo et al,[65] Krause et al,[68] 12 wk	No serious risk of bias	Serious inconsistency[a]	No serious indirectness	No serious imprecision	Undetected	⊕⊕⊕⊖ Moderate[a] due to inconsistency	278/445 (62.5)	423/1061 (39.9)	RR, 0.60 (0.54–0.67)	625 per 1000	250 fewer per 1000 (from 206 fewer to 287 fewer)
Failure of adequate abdominal pain response[b] (important outcome; assessed with patient diary)											
4227 (8 RCTs),[c] 12 wk	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	⊕⊕⊕⊕ High	1113/1710 (65.1)	1310/2517 (52.0)	RR, 0.83 (0.79–0.88)	651 per 1000	111 fewer per 1000 (from 78 fewer to 137 fewer)
Failure of adequate urgency response[d] (important outcome): not reported											
Failure of improvement in stool consistency[d] (important outcome): not reported											
Failure of improvement in IBS-QOL[e] (important outcome; assessed with patient diary)											
705 (1 RCT), Cremonini et al, 12 wk	See text[69]										
Ischemic colitis[f] (critical outcome)											
1 observational study, Tong et al,[60] 9 y	See text										1.03 cases per 1000 patient-years
Serious complication of constipation[g] (ie, fecal impaction) (important outcome)											
1 observational study, Tong et al,[60] 9 y	See text										0.25 cases per 1000 patient-years

[a]The I[2] was 95% and therefore was rated down for inconsistency. Some of this heterogeneity may have been due to the fact that the studies by Krause et al[68] and Lembo et al[65] used varying doses of alosetron and varying disease severity for the 2 populations.
[b]This outcome was recalculated using primary data obtained from the sponsor of the study by Krause et al.[68]
[c]The 8 RCTs included Camilleri et al,[61] Bardhan et al,[63] Camilleri et al,[62] Lembo et al,[65] Camilleri et al,[64] Chey et al,[66] Chang et al,[67] and Krause et al.[68]
[d]This outcome could not be systematically analyzed because of differences in the way the data were collected and reported (mean ± SD).
[e]The IBS-QOL is a 30-item scale with 9 domains (emotional, mental health, sleep, energy, physical functioning, food/diet, social functioning, physical role, sexual relations).
[f]Of more than 28,084 patient-years of alosetron exposure, 29 (probable/possible) cases of ischemic colitis were identified, corresponding to a rate of 1.03 cases/1000 patient-years.
[g]Of more than 28,084 patient-years of alosetron exposure, 7 cases of chronic constipation were identified, corresponding to a rate of 0.25 cases/1000 patient-years.

with severe IBS-D. A disease-specific questionnaire, IBS-QOL,[69] was used that evaluated 9 health status dimensions.[70] At least one dose of alosetron was associated with significant improvements in all IBS-QOL dimensions except sexual relations.

A recent study adjudicated postmarketing cases of ischemic colitis and complications of constipation and evaluated temporal trends in alosetron postmarketing safety over 9 years under the risk management plan (2002–2011).[60] The cumulative adjudicated incidence of ischemic colitis was 1.03 cases per 1000 patient-years, which suggested that the incidence of ischemic colitis remained low and stable over time. The adjudicated incidence rate of serious complications of constipation was 0.25 cases per 1000 patient-years and appeared to have declined over time.

> The overall quality of evidence across all critical outcomes for alosetron was moderate.

Discussion

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 one 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.[60] Adequate global relief response was only evaluated in 2 relatively recent studies that enrolled women with more severe IBS-D. Because the critical outcomes for alosetron are adequate global relief response and incidence of ischemic colitis, the overall quality of evidence was moderate. However, the quality of evidence for adequate relief of IBS abdominal pain and discomfort was high based on 8 RCTs. Alosetron showed clinically meaningful improvements in both adequate global relief and abdominal pain responses. Therefore, in women with IBS-D who have frequent or severe abdominal pain and who have failed to respond to conventional therapy, alosetron would be an appropriate treatment to consider. Although the FDA has challenged the ability of a single general item that asks about overall symptoms of IBS, such as the binary end point of adequate relief, to capture whether benefit is achieved in all or only some patients,[28] Spiegel et al showed that this end point has strong construct validity and detected minimal clinically important differences in symptoms in patients with IBS.[71]

Other systematic reviews and meta-analyses have evaluated the efficacy of alosetron in IBS; although the quality of evidence for the overall relief of symptoms of IBS was mainly based on adequate relief of IBS pain and discomfort, they concluded that there is moderate to high-quality evidence that alosetron improves symptoms of IBS compared with placebo.[51,72–77] RCTs have shown beneficial effects of alosetron in patients with IBS-D, 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 while that of ischemic colitis has remained stable.[60]

Question: Should Loperamide Be Used in Patients With IBS-D?

Results

Loperamide is an antidiarrheal agent that is a synthetic opioid receptor agonist; it inhibits peristalsis and antisecretory activity and prolongs intestinal transit time with limited penetrance of the blood-brain barrier. It is approved for the treatment of patients with acute, chronic, and traveler's diarrhea. Two small, double-blind, placebo-controlled trials have evaluated the efficacy of loperamide in patients with IBS.[78,79] Neither defined the diagnostic criteria for IBS but excluded organic gastrointestinal disease. One study[79] evaluated patients with IBS who had alternating bowel habits and used 4 mg of loperamide at bedtime for 3 weeks by monitoring daily symptoms. The other study[78] assessed patients with IBS who had diarrhea over a treatment period of 13 weeks, starting with a 2-mg dose in the evening for 1 week and then giving the patients the option to increase or decrease the dose based on symptom response. Patients remained on an individualized dose ranging from 2 to 8 mg daily in the fifth week until the end of the study. Improvements in symptoms were determined via a telephone interview in the 5th week.[78] Only the study by Hovdenak et al[79] measured the overall symptom response rate in 21 patients with IBS (loperamide, n = 10; placebo, n = 11). Compared with placebo, loperamide was not associated with a lower failure rate of global improvement (RR, 0.73; 95% CI, 0.29–1.86). Based on a placebo failure rate of 54.5%, use of loperamide would result in 147 fewer failures per 1000 (95% CI, 387 fewer to 469 more).

Both studies evaluated adequate abdominal pain and stool consistency.[78,79] Compared with placebo, loperamide showed a lower failure rate of adequate relief of abdominal pain (RR, 0.41; 95% CI, 0.20–0.84). Based on a placebo failure rate of 71.4%, use of loperamide would result in 421 fewer failures per 1000 (95% CI, 114 fewer to 571 fewer). Similarly, loperamide showed a significantly lower failure rate of improvement of stool consistency (RR, 0.06; 95% CI, 0.01–0.43). Based on a placebo failure rate of 71.4%, use of loperamide would result in 671 fewer failures (95% CI, 407 fewer to 707 fewer).

One study measured failure of improvement in urgency.[78] Compared with placebo, the failure rate was not significantly different with loperamide (RR, 0.61; 95% CI, 0.13–2.92). Based on a placebo failure rate of 30%, use of loperamide would result in 117 fewer failures per 1000 (95% CI, 261 fewer to 576 more).[78]

The overall quality of evidence was rated as very low due to serious risk of bias, imprecision, and suspected publication bias. In addition, the body of evidence included only 2 older, very small studies. There were no data

Table 7. Question: Should Loperamide Be Used in Patients With IBS-D?

No. of participants (no. of studies), authors, follow-up	Quality assessment						Summary of findings				
							Study event rates (%)			Anticipated absolute effects	
	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	With placebo	With loperamide	Relative effect (95% CI)	Risk with placebo	Risk difference with loperamide (95% CI)
Failure of adequate global relief response (overall) (critical outcome; assessed with patient diary)											
21 (1 RCT), Hovdenak et al,[79] 3 wk	Serious risk of bias[a]	No serious inconsistency	No serious indirectness	Serious imprecision[b]	Publication bias strongly suspected[c]	⊕⊖⊖⊖ Very low[a,b,c] due to risk of bias, imprecision, publication bias	6/11 (54.5)	4/10 (40.0)	RR, 0.73 (0.29–1.86)	545 per 1000	147 fewer per 1000 (from 387 fewer to 469 more)
Failure of adequate abdominal pain response (important outcome; assessed with patient diary)											
42 (2 RCTs), Lavo et al,[78] Hovdenak et al,[79] 3–5 wk	Serious risk of bias[a]	No serious inconsistency	No serious indirectness	Serious imprecision[d]	Publication bias strongly suspected[c]	⊕⊖⊖⊖ Very low[a,c,d] due to risk of bias, imprecision, publication bias	15/21 (71.4)	6/21 (28.6)	RR, 0.41 (0.20–0.84)	714 per 1000	421 fewer per 1000 (from 114 fewer to 571 fewer)
Failure of improvement in urgency (important outcome)											
21 (1 RCT), Lavo et al,[78] 5 wk	Serious risk of bias[a]	No serious inconsistency	No serious indirectness	Serious imprecision[d]	Publication bias strongly suspected[c]	⊕⊖⊖⊖ Very low[a,c,d] due to risk of bias, imprecision, publication bias	3/10 (30.0)	2/11 (18.2)	RR, 0.61 (0.13–2.92)	300 per 1000	117 fewer per 1000 (from 261 fewer to 576 more)
Failure of improvement in stool consistency (important outcome)											
42 (2 RCTs), Lavo et al,[78] Hovdenak et al,[79] 3–5 wk	Serious risk of bias[a]	No serious inconsistency	No serious indirectness	No serious imprecision	Publication bias strongly suspected[c]	⊕⊕⊖⊖ Low[a,c] due to risk of bias, publication bias	15/21 (71.4)	0/21 (0.0)	RR, 0.06 (0.01–0.43)	714 per 1000	671 fewer per 1000 (from 407 fewer to 707 fewer)
Adverse events leading to treatment discontinuation (important outcome): not reported											

[a]This was an old study (published in 1987) and did not explicitly describe the methods of the study; thus, the risk of bias was unclear.
[b]The upper boundary of the CI did not cross our minimal clinically important effect of at least 10%, and the CI was very wide due to few events and small sample size.
[c]Very few published studies in the literature (only 2 studies were found from 1987) reported on these patient-important outcomes in patients with IBS.
[d]The CI is very wide due to few events and small sample size.

available to assess the effect of loperamide on IBS-QOL or adverse events leading to treatment discontinuation.

> **The overall quality of evidence across all critical outcomes for loperamide was very low.**

Discussion

The quality of the evidence for loperamide in the treatment of patients with IBS was very low. There was a lack of beneficial effect on global improvement of symptoms of IBS and urgency. There was significant improvement in abdominal pain and stool consistency. However, this review was based on only 2 very small studies. Improvements in these symptoms occurred within 3 to 5 weeks of starting treatment, and details of how this was determined were poorly described. 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, but there is a lack of data evaluating its efficacy in relieving individual gastrointestinal symptoms, such as abdominal pain, in IBS. It is also not clear if loperamide should be only recommended in IBS-D or also in IBS-M, presumably during a diarrheal phase. The optimal dose and method of using loperamide (eg, as needed, daily, after a certain number of diarrheal stools, and so on) is not known and potentially can vary between patients based on their symptom patterns. The likelihood that the efficacy of an over-the-counter remedy for diarrhea will be studied in large IBS clinical trials is low.

Systematic reviews were previously conducted on the efficacy of loperamide in patients with IBS. The American College of Gastroenterology Task Force also rated the quality of evidence that loperamide relieves the global symptoms in IBS as very low.[51] In the British Society of Gastroenterology guidelines for the practice management of IBS, the quality of evidence for loperamide in patients with IBS-D was considered to be high based on the statement that "further research is very unlikely to change our confidence in the estimate effect."[76] Loperamide was believed to have a net benefit because it does more good than harm.

Question: Should TCAs Be Used in Patients With IBS?

Results

TCAs are commonly used to treat patients with neuropathic pain. Their mechanism of action is not completely understood but appears to include peripheral and central (ie, supraspinal and spinal) effects. Eight placebo-controlled RCTs in 523 patients (TCAs, n = 297; placebo, n = 122) were included in this review.[80–88] There was uncertainty regarding allocation concealment and blinding in many of the RCTs. One trial[80–88] enrolled only patients with IBS-D, whereas the other trials included multiple 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 150 mg; most studies used >50 mg/day. Global assessments differed among the trials. Abdominal pain response was assessed in 4 trials[83,87–89] (TCAs, n = 189; placebo, n = 131).

Compared with placebo, TCAs showed a lower failure rate of global symptom relief (RR, 0.67; 95% CI, 0.54–0.82). Based on a placebo failure rate of 61%, use of TCAs would result in 202 fewer failures per 1000 (95% CI, 110 fewer to 281 fewer). The quality of evidence was rated as low due to indirectness and a very serious potential risk of bias. Compared with placebo, TCAs showed a significantly lower failure rate of abdominal pain relief (RR, 0.76; 95% CI, 0.61–0.94). Based on a placebo failure rate of 55.7%, use of TCAs would result in 134 fewer failures per 1000 (95% CI, 33 fewer to 217 fewer). The quality of evidence was rated as low for the beneficial outcomes due to the potential for risk of bias, indirectness, and imprecision because the upper boundary of the CI did not cross our threshold for a clinically meaningful difference. For adverse events, we used data from 23 clinical trials in depression because long-term high-quality data with TCAs in patients with IBS were not available.[90] In these trials compared with placebo, TCAs showed a significantly higher rate of withdrawals due to adverse effects (RR, 2.11; 95% CI, 1.35–3.28). Based on a placebo withdrawal rate of 3.8%, use of TCAs would result in 42 more withdrawals per 1000 (95% CI, 13 more to 87 more). The quality of the evidence for this outcome was also low (we rated down for potential risk of bias and indirectness because a non-IBS population was used). The other patient-important outcomes could not be assessed based on the available data.

> **The overall quality of evidence across all critical outcomes for TCAs was low.**

Discussion

Although TCAs were associated with significant benefits for adequate global relief and abdominal pain relief response compared with placebo, only the global relief response met the threshold for being clinically meaningful. The overall quality of evidence for TCAs was rated as low due to the serious risk of bias given the uncertainty regarding allocation concealment and blinding in many of the RCTs. A Cochrane review[80] and a meta-analysis[91] that included additional trials also found evidence to support the use of TCAs in patients with IBS for global assessment, abdominal pain, and symptom score. TCAs may take several weeks to work. Their effects on symptoms of IBS appear to be independent of effects on depression. Most studies evaluated higher doses of TCAs (ie, ≥50 mg) than frequently used in clinical practice, although amitriptyline 10 mg at bedtime showed efficacy in patients with IBS-D in one study.[70]

Table 8. Question: Should TCAs Be Used in Patients With IBS?

No. of participants (no. of studies), authors, follow-up	Quality assessment						Summary of findings				
	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With placebo	With TCAs		Risk with placebo	Risk difference with TCAs (95% CI)
Failure of adequate global relief response[a] (critical outcome; assessed with patient diary)											
523 (8 RCTs),[b] 6–12 wk	Serious risk of bias[c]	No serious inconsistency	Serious indirectness[d]	No serious imprecision	Undetected	⊕⊕⊖⊖Low[c,d] due to risk of bias and indirectness	138/226 (61.1)	122/297 (41.1)	RR, 0.67 (0.54–0.82)	611 per 1000	202 fewer per 1000 (from 110 fewer to 281 fewer)
Failure of adequate abdominal pain response[a] (important outcome; assessed with patient diary)											
320 (4 RCTs), Drossman et al,[83] Heefner et al,[89] Vahedi et al,[87] Vij et al,[88] 6–12 wk	Serious risk of bias[c]	No serious inconsistency	No serious indirectness	Serious imprecision[e]	Undetected	⊕⊕⊖⊖Low[e] due to risk of bias and imprecision	73/131 (55.7)	80/189 (42.3)	RR, 0.76 (0.61–0.94)	557 per 1000	134 fewer per 1000 (from 33 fewer to 217 fewer)
Adverse effects leading to treatment discontinuation[f] (important outcome)											
1438 (23 RCTs),[f] 4–52 wk	Serious risk of bias[c]	No serious inconsistency	Serious indirectness[g]	No serious imprecision	Undetected	⊕⊕⊖⊖Low[c] due to risk of bias and indirectness	26/681 (3.8)	65/757 (8.6)	RR, 2.11 (1.35–3.28)	38 per 1000	42 more per 1000 (from 13 more to 87 more)

[a]The Cochrane systematic review by Ruepert et al[80] was used: 8 RCTs informed the outcome "failure of adequate global relief," and 4 RCTs informed the outcome "failure of adequate abdominal pain response."

[b]The 8 RCTs included Bergmann et al,[81] Boerner et al,[82] Drossman et al,[83] Myren et al,[84] Nigam et al,[85] Talley et al,[86] Vahedi et al,[87] and Vij et al.[88]

[c]These data were from older studies in which there was considerable uncertainty regarding appropriate adequate allocation concealment and blinding.

[d]There were different populations and different doses of the intervention used across the studies.

[e]The upper boundary of the CI did not cross our minimal clinically important effect of at least 10%.

[f]The Cochrane systemic review by Furukawa et al[90] was used for this outcome (all 23 RCTs that informed this outcome could not be listed but are referenced in the Cochrane review).

[g]In these 23 RCTs, the population consisted of patients with major depression and the doses used were higher than those currently used for the treatment of IBS.

Question: Should SSRIs Be Used in Patients With IBS?

Results

SSRIs are approved for the treatment of some affective disorders, including depression, but are also often used in clinical practice to treat patients with 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. These agents are also believed to activate descending pain inhibitory pathways.[92] The efficacy of SSRIs in IBS was studied in 5 RCTs, which enrolled 281 patients (SSRIs, n = 143; placebo, n = 138).[79,86,93–95] All were blinded and likely achieved allocation concealment. Two studies used Rome I criteria, and the other 3 used Rome II criteria. There was a mixture of all 3 main bowel habit subtypes in 4 of the studies, although the largest group was IBS-D in 3 of them. One study did not report IBS bowel habit subtypes. Some effort was made in each study to exclude patients with evidence of current psychiatric disease. The duration of treatment was 6 weeks in one study,[93] 8 weeks in another,[94] and 12 weeks in 3 trials.[86,95,96] Different SSRIs were evaluated: fluoxetine 20 mg daily,[93] paroxetine 10 mg daily but could be increased,[96] paroxetine CR 12.5 to 50 mg daily,[95] and citalopram at a starting dose of 20 mg that was increased to 40 mg daily after 2[86] or 4[94] weeks in 2 studies.

The 5 RCTs performed a global assessment, although they differed between studies: IBS symptom relief (n = 1),[93] adequate relief of symptoms of IBS (n = 2),[86,94] Global Clinical Impression-Improvement Scale (n = 1),[95] and overall well-being and not specifically symptoms of IBS (n = 1).[96] Compared with placebo, SSRIs showed a nonsignificant lower failure rate of symptom relief (RR, 0.74; 95% CI, 0.52–1.06). Based on a placebo failure rate of 65.2%, use of SSRIs would result in 170 fewer failures per 1000 (95% CI, 313 fewer to 39 more). The quality of evidence was rated as low due to serious inconsistency and imprecision (CI includes both benefit and harm).

Four studies evaluated failure of adequate abdominal pain response (SSRIs, n = 96; placebo, n = 101).[87,93,96,97] Abdominal pain was assessed differently in each study. Two studies used a rating scale of discomfort or severity, and a third study graded the degree of improvement of abdominal pain. Compared with placebo, SSRIs did not show a significantly lower failure rate (RR, 0.63; 95% CI, 0.35–1.12). Based on a placebo failure rate of 72.3%, use of SSRIs would result in 267 fewer failures per 1000 (95% CI, 470 fewer to 87 more). The quality of evidence for this outcome was rated as low due to serious inconsistency and imprecision (CI includes both benefit and harm). The other critical or important outcomes could not be assessed based on the available data.

Two studies compared changes in IBS-specific QOL between the SSRI and placebo groups but reported either a percentage change within a domain or mean scores and not overall responder rates.[94,96] One study found a significantly greater improvement in food avoidance score,[96] and the other study did not detect any differences.[94] There are no long-term, high-quality data with SSRIs in IBS or depression to assess adverse events leading to treatment withdrawal.

> The overall quality of evidence across all critical outcomes for SSRIs was low.

Discussion

Based on the studies included in this review, SSRIs do not significantly improve global symptoms or abdominal pain in patients with IBS, although the quality of evidence is low. A recent Cochrane meta-analysis found that SSRIs had a statistically significant benefit for improvement in global assessment, but their effectiveness may depend on the individual characteristics of a patient.[79] However, this meta-analysis did not include one of the studies that was included in this analysis. The American College of Gastroenterology Task Force systematic review and meta-analysis determined that there is high-quality evidence to support the efficacy of antidepressants (collectively TCAs and SSRIs) in relieving global symptoms of IBS and reducing abdominal pain compared with placebo.[51,91] This meta-analysis differed from ours because their assessment was based on pooling studies that reported either a global assessment of symptoms of IBS or improvement in abdominal pain. There are insufficient data to determine in a more comprehensive manner the efficacy of SSRIs on individual symptoms of IBS and disease-specific QOL. Nonetheless, disease-specific QOL did not significantly improve overall based on limited data and a small sample size.

Multiple factors, including those arising from central and peripheral processes, contribute to the severity of IBS. The Rome severity working team defined IBS severity as a "biopsychosocial composite of patient reported gastrointestinal and extra-intestinal symptoms, degree of disability, and illness related perceptions and behaviors."[42] SSRIs may improve the perception of overall symptoms of IBS and well-being by improving gastrointestinal symptoms, coexistent alterations in mood, and extraintestinal symptoms.[92] 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, but clinical trials are needed.

Question: Should Antispasmodics Be Used in Patients With IBS?

Results

Antispasmodics are commonly used in clinical practice to alleviate abdominal spasms and cramps associated with IBS. Although a pharmacologically diverse class, the mechanism of action by which antispasmodics are believed to relieve symptoms of IBS (particularly abdominal pain and cramps) is through reduction in smooth muscle contraction (ie, spasms), but they may also have effects on visceral

Table 9. Question: Should SSRIs Be Used in Patients With IBS?

		Quality assessment					Summary of findings				
							Study event rates (%)			Anticipated absolute effects	
No. of participants (no. of studies), follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	With placebo	With SSRI	Relative effect (95% CI)	Risk with placebo	Risk difference with SSRI (95% CI)
Failure of adequate global relief response (critical outcome; assessed with patient diary)											
281 (5 RCTs),[a] 6–12 wk	No serious risk of bias	Serious inconsistency[b]	No serious indirectness	Serious imprecision[c]	Undetected	⊕⊕⊖⊖ Low[b,c] due to inconsistency and imprecision	90/138 (65.2)	65/143 (45.5)	RR, 0.74 (0.52–1.06)	652 per 1000	170 fewer per 1000 (from 313 fewer to 39 more)
Failure of adequate abdominal pain response (important outcome; assessed with patient diary)											
197 (4 RCTs),[d] 6–12 wk	No serious risk of bias	Serious inconsistency[b]	No serious indirectness	Serious imprecision[c]	Undetected	⊕⊕⊖⊖ Low[b,c] due to inconsistency and imprecision	73/101 (72.3)	51/96 (53.1)	RR, 0.63 (0.35–1.12)	723 per 1000	267 fewer per 1000 (from 470 fewer to 87 more)
Adverse events leading to treatment discontinuation[e] (important outcome): not reported											

[a]The 5 RCTs included Kuiken et al,[93] Ladabaum et al,[94] Masand et al,[95] Tabas et al,[96] and Talley et al.[86]
[b]We rated down for inconsistency because the I^2 was 54%.
[c]The upper boundary of the CI did not cross our minimal clinically important threshold of 10%.
[d]The 4 RCTs included Kuiken et al,[93] Tabas et al,[96] Tack et al,[97] and Vahedi et al.[87]
[e]The I^2 was 80%, and we therefore rated down for inconsistency.

hypersensitivity.[98] Of the antispasmodics studied, only hyoscyamine, dicyclomine, and peppermint oil are available in the United States. We identified 22 RCTs evaluating 2983 patients with IBS (antispasmodics, n = 1008; placebo, n = 1975).[79] Twelve different antispasmodics were assessed. There was considerable variation between the studies concerning diagnostic and inclusion criteria, dosing schedule, and study end points. Most studies predate the Rome criteria and therefore differed on the definitions of IBS. In general, IBS subtypes were not differentiated in the analysis. Comparison between antispasmodics could not be performed.

Antispasmodics demonstrate clinically meaningful improvement in global symptoms of IBS. Compared with placebo, antispasmodics showed a lower rate of failure of adequate global relief of symptoms of IBS (22 RCTs) with an RR of 0.67 (95% CI, 0.55–0.80). Based on a placebo failure rate of 60.0%, antispasmodics would result in 200 fewer failures per 1000 (95% CI, 121 fewer to 273 fewer). The overall quality of evidence, however, was low due to the serious risk of bias and publication bias. Likewise, compared with placebo, antispasmodics showed improvement in abdominal pain with an RR of 0.74 (95% CI, 0.59–0.93). Based on a placebo failure rate of 53.6%, antispasmodics would result in 139 fewer adequate abdominal pain failures per 1000 (95% CI, 38 fewer to 220 fewer). For this outcome, the quality of 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 given 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 lack of consistent reporting.

> **The overall quality of evidence across all critical outcomes for antispasmodics was low.**

Discussion

Antispasmodics include a wide array of pharmacological therapies that are purported to reduce colonic smooth muscle spasm. Most have been used clinically for many years and have not been subjected to rigorous large multicenter trials. We identified 12 different antispasmodics in 22 RCTs involving 1283 patients with IBS. Of the studies of antispasmodics, only hyoscyamine, dicyclomine, and peppermint oil are available in the United States. There was considerable variation among the trials, and in general the quality of the studies was low. Nevertheless, improvement was demonstrated by antispasmodics compared with placebo for global relief and abdominal pain, although the latter did not meet our criteria for being clinically meaningful. A recent Cochrane review[80] found a beneficial effect for antispasmodics over placebo for improvement in abdominal pain and global assessment. It is not clear if antispasmodics

are more efficacious in specific IBS subtypes, but regular use in patients with constipation may be limited due to the anticholinergic effects. Although these medications are often recommended for treatment of postprandial symptoms in patients with IBS, this has not been specifically studied in RCTs.

Summary and Conclusions

In this technical review, we evaluated the efficacy and safety of pharmacological treatment of patients with IBS. Nine treatments were assessed and included treatments that have been studied in high-quality multicenter RCTs (such as linaclotide, lubiprostone, rifaximin, and alosetron) and those that have been studied in smaller or less rigorous trials (such as antispasmodics, TCAs, SSRIs, loperamide, and PEG). We evaluated the effect of treatment on global assessments, which were considered critical outcomes, as well as individual symptom responses, health-related QOL, and adverse events leading to treatment withdrawal, which were considered important outcomes. However, responder rates were not universally available; therefore, some outcomes could not be consistently addressed for all treatments. Using the GRADE process, we aimed for greater transparency in rating the quality of evidence and for greater explicitness about the comparators used and outcomes assessed. To weigh the trade-offs involved with different interventions, the GRADE process presents the absolute risk differences for both beneficial outcomes and harms. In the following text, we discuss our findings on the effectiveness and safety of IBS therapies, compare and explain the differences between our conclusions and those in other published guidelines, and suggest areas of future research.

Review of the evidence for 9 pharmacological treatments for patients with IBS showed that across all outcomes, evidence was high for linaclotide; moderate for lubiprostone, rifaximin, and alosetron; low for TCAs, SSRIs, and PEG; and very low for loperamide and antispasmodics. The methodology of our technical review differed from others because we rated the evidence across a range of outcomes that measured both risk and benefit and separately assessed response rates for global symptoms and abdominal pain. Furthermore, we weighed the evidence more on the critical outcomes (eg, global relief) than important outcomes (eg, individual symptoms, adverse events). We also took into account whether the difference between active treatment and placebo was clinically meaningful (ie, ≥10% improvement). A lower quality of evidence may reflect a lack of sufficient data to determine efficacy rather than a definitive lack of efficacy.

This technical review highlights the limitations in the available data and gaps in our current knowledge of IBS. There is significant heterogeneity between studies, even between those studying the same class of medication (eg, antispasmodics, antidepressants). This is due to a number of factors. IBS lacks a diagnostic biomarker, which results in the diagnosis being dependent on symptom-based diagnostic criteria, which have evolved over time and therefore

Table 10. Question: Should Antispasmodics Be Used in Patients With IBS?

	Quality assessment						Summary of findings				
							Study event rates (%)			Anticipated absolute effects	
No. of participants (no. of studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	With placebo	With antispasmodics	Relative effect (95% CI)	Risk with placebo	Risk difference with antispasmodics (95% CI)
Failure of adequate global relief response (critical outcome; assessed with patient diary)											
1983 (22 RCTs)	Serious risk of bias[a]	No serious inconsistency[b]	No serious indirectness	No serious imprecision	Publication bias strongly suspected[c]	⊕⊕⊝⊝ Low[a,b,c] due to risk of bias, publication bias	591/1975 (60.6)	429/1008 (42.6)	RR, 0.67 (0.55–0.80)	606 per 1000	200 fewer per 1000 (from 121 fewer to 273 fewer)
Failure of adequate abdominal pain response (important outcome; assessed with patient diary)											
1392 (13 RCTs)	Serious risk of bias[a]	No serious inconsistency[d]	No serious indirectness	Serious imprecision[e]	Publication bias strongly suspected[c]	⊕⊝⊝⊝ Very low[a,d,e] due to risk of bias, imprecision, publication bias	373/696 (53.6)	289/696 (41.5)	RR, 0.74 (0.59–0.93)	536 per 1000	139 fewer per 1000 (from 38 fewer to 220 fewer)
Adverse events leading to treatment discontinuation (important outcome): not reported											

[a]Risk of bias was unclear in many of the studies (particularly the older ones) with respect to adequate allocation concealment and blinding.
[b]The I^2 was 77%, which suggested moderate heterogeneity amongst the studies; however, we did not rate down for inconsistency because much of the heterogeneity could be explained by the differences in classes and dose of antispasmodics studied.
[c]The funnel plot showed asymmetry with smaller negative trials likely not being published.
[d]The I^2 was 67%, but we did not rate down for inconsistency (see b).
[e]The upper boundary of the CI did not cross our minimal clinically important threshold of 10%.

differ between studies. There is also no universally agreed primary end point for IBS that has been developed with good measurement science as directed by the FDA guidance and adequately measures the treatment benefit of the most significant signs and symptoms of IBS. Therefore, different primary end points have been used in IBS clinical trials over the years. Relatively recently, the FDA proposed composite primary end points for IBS-C and IBS-D, although only a few newer studies have instituted this in their clinical trials so far. Another area in which there is a gap in knowledge is IBS-M, which is arguably the most prevalent of the IBS subtypes but the least well characterized.[99] Thus, there are no proposed or validated primary end points for this subtype. Clinical trials often enroll a selected population of patients in part to remove confounders (eg, medication, comorbidities), and therefore the results are not necessarily applicable to all patients with IBS. Another unmet need in IBS clinical trials is the lack of a single biomarker that can exemplify the different pathophysiological mechanisms of IBS or one that can reliably predict treatment response for medications that have different predominant mechanisms of action (eg, normalizing bowel habits, visceral analgesic). Lastly, technical reviews on nonpharmacological interventions were beyond the scope of this review. Dietary modification, behavioral treatments, and probiotics may be beneficial in patients with IBS and can be considered on an individual basis.

Despite these limitations and knowledge gaps, progress is being made that will lead to greater harmonization and quality of clinical trial data in IBS. The advent of guidance and oversight for patient reported outcomes (PRO) development, IBS PROs, and clinical trial methodology will help shepherd the attainment of consistently high-quality data in which we can more accurately and confidently determine the true efficacy of IBS therapies. In addition, there are ongoing efforts to develop a valid PRO that will be acceptable to regulatory agencies and more reliably capture the treatment benefit of the most bothersome and predominant signs and symptoms. Technical reviews provide evidence of treatment efficacy and harm in a structured manner, and while clinicians should use this information as a basis for guiding therapy, they also need to integrate other clinically relevant information, such as a patient's values and preferences, when making treatment decisions in an individual patient.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org and at http://dx.doi.org/10.1053/j.gastro.2014.09.002.

References

1. Longstreth GF, Thompson WG, Chey WD, et al. Functional bowel disorders. Gastroenterology 2006;130:1480–1491.
2. Lovell RM, Ford AC. Effect of gender on prevalence of irritable bowel syndrome in the community: systematic review and meta-analysis. Am J Gastroenterol 2012;107:991–1000.
3. Hungin AP, Chang L, Locke GR, et al. Irritable bowel syndrome in the United States: prevalence, symptom patterns and impact. Aliment Pharmacol Ther 2005;21:1365–1375.
4. Hungin AP, Whorwell PJ, Tack J, et al. The prevalence, patterns and impact of irritable bowel syndrome: an international survey of 40,000 subjects. Aliment Pharmacol Ther 2003;17:643–650.
5. Drossman DA, Camilleri M, Mayer EA, et al. AGA technical review on irritable bowel syndrome. Gastroenterology 2002;123:2108–2131.
6. Pare P, Gray J, Lam S, et al. Health-related quality of life, work productivity, and health care resource utilization of subjects with irritable bowel syndrome: baseline results from LOGIC (Longitudinal Outcomes Study of Gastrointestinal Symptoms in Canada), a naturalistic study. Clin Ther 2006;28:1726–1735; discussion 1710–1711.
7. Hammer J, Eslick GD, Howell SC, et al. Diagnostic yield of alarm features in irritable bowel syndrome and functional dyspepsia. Gut 2004;53:666–672.
8. Vanner SJ, Depew WT, Paterson WG, et al. Predictive value of the Rome criteria for diagnosing the irritable bowel syndrome. Am J Gastroenterol 1999;94:2912–2917.
9. Dassopoulos T, Inadomi JM, Lewis JD, et al. The development of clinical guidelines by the American Gastroenterological Association. Gastroenterology 2010;138:417–418.
10. Inadomi JM, Weinberg DS. How to recognize a good guideline. Gastroenterology 2013;145:1179–1181.
11. Sultan S, Falck-Ytter Y, Inadomi JM. The AGA institute process for developing clinical practice guidelines part one: grading the evidence. Clin Gastroenterol Hepatol 2013;11:329–332.
12. Guyatt GH, Oxman AD, Vist G, et al. GRADE guidelines: 4. Rating the quality of evidence—study limitations (risk of bias). J Clin Epidemiol 2011;64:407–415.
13. Guyatt GH, Oxman AD, Sultan S, et al. GRADE guidelines: 9. Rating up the quality of evidence. J Clin Epidemiol 2011;64:1311–1316.
14. Guyatt GH, Oxman AD, Schunemann HJ, et al. GRADE guidelines: a new series of articles in the Journal of Clinical Epidemiology. J Clin Epidemiol 2011;64:380–382.
15. Guyatt GH, Oxman AD, Montori V, et al. GRADE guidelines: 5. Rating the quality of evidence—publication bias. J Clin Epidemiol 2011;64:1277–1282.
16. Guyatt GH, Oxman AD, Kunz R, et al. GRADE guidelines: 7. Rating the quality of evidence—inconsistency. J Clin Epidemiol 2011;64:1294–1302.
17. Guyatt GH, Oxman AD, Kunz R, et al. GRADE guidelines: 8. Rating the quality of evidence—indirectness. J Clin Epidemiol 2011;64:1303–1310.
18. Guyatt GH, Oxman AD, Kunz R, et al. GRADE guidelines 6. Rating the quality of evidence—imprecision. J Clin Epidemiol 2011;64:1283–1293.
19. Guyatt GH, Oxman AD, Kunz R, et al. GRADE guidelines: 2. Framing the question and deciding on important outcomes. J Clin Epidemiol 2011;64:395–400.

20. Guyatt GH, Thorlund K, Oxman AD, et al. GRADE guidelines: 13. Preparing summary of findings tables and evidence profiles-continuous outcomes. J Clin Epidemiol 2013;66:173–183.

21. Guyatt GH, Oxman AD, Schunemann HJ. GRADE guidelines—an introduction to the 10th-13th articles in the series. J Clin Epidemiol 2013;66:121–123.

22. Guyatt GH, Oxman AD, Santesso N, et al. GRADE guidelines: 12. Preparing summary of findings tables-binary outcomes. J Clin Epidemiol 2013;66:158–172.

23. Guyatt G, Oxman AD, Sultan S, et al. GRADE guidelines: 11. Making an overall rating of confidence in effect estimates for a single outcome and for all outcomes. J Clin Epidemiol 2013;66:151–157.

24. Brunetti M, Shemilt I, Pregno S, et al. GRADE guidelines: 10. Considering resource use and rating the quality of economic evidence. J Clin Epidemiol 2013;66:140–150.

25. Andrews JC, Schunemann HJ, Oxman AD, et al. GRADE guidelines: 15. Going from evidence to recommendation-determinants of a recommendation's direction and strength. J Clin Epidemiol 2013;66:726–735.

26. Andrews J, Guyatt G, Oxman AD, et al. GRADE guidelines: 14. Going from evidence to recommendations: the significance and presentation of recommendations. J Clin Epidemiol 2013;66:719–725.

27. Lewis SJ, Heaton KW. Stool form scale as a useful guide to intestinal transit time. Scand J Gastroenterol 1997; 32:920–924.

28. Guidance for industry: irritable bowel syndrome-clinical evaluation of drugs for treatment. US Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER) 2012. Available at http://www.fda.gov/downloads/drugs/guidances/ucm205269.pdf.

29. Redelmeier DA, Guyatt GH, Goldstein RS. Assessing the minimal important difference in symptoms: a comparison of two techniques. J Clin Epidemiol 1996;49:1215–1219.

30. Thomson D, Russell K, Becker L, et al. The evolution of a new publication type: steps and challenges of producing overviews of reviews. Res Synth Method 2010;1:198–211.

31. Review Manager (RevMan) version 5.1. Copenhagen, Denmark: The Nordic Cochrane Center, The Cochran Collaboration, 2011.

32. Bryant AP, Busby RW, Bartolini WP, et al. Linaclotide is a potent and selective guanylate cyclase C agonist that elicits pharmacological effects locally in the gastrointestinal tract. Life Sci 2010;86:760–765.

33. Andresen V, Camilleri M, Busciglio IA, et al. Effect of 5 days linaclotide on transit and bowel function in females with constipation-predominant irritable bowel syndrome. Gastroenterology 2007;133:761–768.

34. 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′-monophosphate. Gastroenterology 2013;145:1334–1346. e1–11.

35. Videlock EJ, Cheng V, Cremonini F. Effects of linaclotide in patients with irritable bowel syndrome with constipation or chronic constipation: a meta-analysis. Clin Gastroenterol Hepatol 2013;11:1084–1092.e3; quiz e68.

36. 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; 107:1702–1712.

37. Rao S, Lembo AJ, Shiff SJ, 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; quiz 1725.

38. Johnston JM, Kurtz CB, Macdougall JE, et al. Linaclotide improves abdominal pain and bowel habits in a phase IIb study of patients with irritable bowel syndrome with constipation. Gastroenterology 2010;139:1877–1886.e2.

39. Patrick DL, Drossman DA, Frederick IO, et al. Quality of life in persons with irritable bowel syndrome: Development of a new measure. Dig Dis Sci 1998;43:400–411.

40. Macdougall JE, Johnston JM, Lavins BJ, et al. An evaluation of the FDA responder endpoint for IBS-C clinical trials: analysis of data from linaclotide phase 3 clinical trials. Neurogastroenterol Motil 2013;25:481–486.

41. Lacy BE, Lembo AJ, Macdougall JE, et al. Responders vs clinical response: a critical analysis of data from linaclotide phase 3 clinical trials in IBS-C. Neurogastroenterol Motil 2014;26:326–333.

42. Drossman DA, Chang L, Bellamy N, et al. Severity in irritable bowel syndrome: a Rome Foundation Working Team report. Am J Gastroenterol 2011;106:1749–1759; quiz 1760.

43. Spiegel B, Strickland A, Naliboff BD, et al. Predictors of patient-assessed illness severity in irritable bowel syndrome. Am J Gastroenterol 2008;103:2536–2543.

44. Spiegel BM, Gralnek IM, Bolus R, et al. Clinical determinants of health-related quality of life in patients with irritable bowel syndrome. Arch Intern Med 2004;164:1773–1780.

45. Drossman DA, Chang L, Schneck S, et al. A focus group assessment of patient perspectives on irritable bowel syndrome and illness severity. Dig Dis Sci 2009;54:1532–1541.

46. Camilleri M, Bharucha AE, Ueno R, et al. Effect of a selective chloride channel activator, lubiprostone, on gastrointestinal transit, gastric sensory, and motor functions in healthy volunteers. Am J Physiol Gastrointest Liver Physiol 2006;290:G942–G947.

47. 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;29:329–341.

48. Johanson JF, Drossman DA, Panas R, et al. Clinical trial: phase 2 study of lubiprostone for irritable bowel syndrome with constipation. Aliment Pharmacol Ther 2008;27:685–696.

49. Chey WD, Drossman DA, Johanson JF, et al. Safety and patient outcomes with lubiprostone for up to 52 weeks in

patients with irritable bowel syndrome with constipation. Aliment Pharmacol Ther 2012;35:587–599.

50. 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;108:1508–1515.

51. 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; quiz S27.

52. Pimentel M, Morales W, Chua K, et al. Effects of rifaximin treatment and retreatment in nonconstipated IBS subjects. Dig Dis Sci 2011;56:2067–2072.

53. Pimentel M, Lembo A, Chey WD, et al. Rifaximin therapy for patients with irritable bowel syndrome without constipation. N Engl J Med 2011;364:22–32.

54. Menees SB, Maneerattannaporn M, Kim HM, et al. The efficacy and safety of rifaximin for the irritable bowel syndrome: a systematic review and meta-analysis. Am J Gastroenterol 2012;107:28–35; quiz 36.

55. Lembo A, Zakko SF, Ferreira NL, et al. Rifaximin for the treatment of diarrhea-associated irritable bowel syndrome: short term treatment leading to long-term sustained response (T1390). Gastroenterology 2008;134(suppl 1). A-545.

56. Pimentel M, Park S, Mirocha J, et al. The effect of a nonabsorbed oral antibiotic (rifaximin) on the symptoms of the irritable bowel syndrome: a randomized trial. Ann Intern Med 2006;145:557–563.

57. Sharara AI, Aoun E, Abdul-Baki H, et al. A randomized double-blind placebo-controlled trial of rifaximin in patients with abdominal bloating and flatulence. Am J Gastroenterol 2006;101:326–333.

58. Efficacy and Safety of Repeat Treatment with Rifaximin for Diarrhea-Predominant Irritable Bowel Syndrome (IBS-D): Results of the TARGET 3 Study Lembo, Pimentel, Rao, Schoenfeld, Cash, Weinstock, Golden, Paterson, Bortey, Forbes, American Journal of Gastroenterology, 109 (10) abstract.

59. Jarcho JM, Chang L, Berman M, et al. Neural and psychological predictors of treatment response in irritable bowel syndrome patients with a 5-HT3 receptor antagonist: a pilot study. Aliment Pharmacol Ther 2008; 28:344–352.

60. Tong K, Nicandro JP, Shringarpure R, et al. A 9-year evaluation of temporal trends in alosetron postmarketing safety under the risk management program. Therap Adv Gastroenterol 2013;6:344–357.

61. Camilleri M, Mayer EA, Drossman DA, et al. Improvement in pain and bowel function in female irritable bowel patients with alosetron, a 5-HT3 receptor antagonist. Aliment Pharmacol Ther 1999;13:1149–1159.

62. Camilleri M, Northcutt AR, Kong S, et al. Efficacy and safety of alosetron in women with irritable bowel syndrome: a randomised, placebo-controlled trial. Lancet 2000;355:1035–1040.

63. Bardhan KD, Bodemar G, Geldof H, et al. A double-blind, randomized, placebo-controlled dose-ranging study to evaluate the efficacy of alosetron in the treatment of irritable bowel syndrome. Aliment Pharmacol Ther 2000; 14:23–34.

64. Camilleri M, Chey WY, Mayer EA, et al. A randomized controlled clinical trial of the serotonin type 3 receptor antagonist alosetron in women with diarrhea-predominant irritable bowel syndrome. Arch Intern Med 2001;161:1733–1740.

65. Lembo T, Wright RA, Bagby B, et al. Alosetron controls bowel urgency and provides global symptom improvement in women with diarrhea-predominant irritable bowel syndrome. Am J Gastroenterol 2001;96: 2662–2670.

66. Chey WD, Chey WY, Heath AT, et al. Long-term safety and efficacy of alosetron in women with severe diarrhea-predominant irritable bowel syndrome. Am J Gastroenterol 2004;99:2195–2203.

67. Chang L, Ameen VZ, Dukes GE, et al. A dose-ranging, phase II study of the efficacy and safety of alosetron in men with diarrhea-predominant IBS. Am J Gastroenterol 2005;100:115–123.

68. Krause R, Ameen V, Gordon SH, et al. A randomized, double-blind, placebo-controlled study to assess efficacy and safety of 0.5 mg and 1 mg alosetron in women with severe diarrhea-predominant IBS. Am J Gastroenterol 2007;102:1709–1719.

69. Hahn BA, Kirchdoerfer LJ, Fullerton S, et al. Evaluation of a new quality of life questionnaire for patients with irritable bowel syndrome. Aliment Pharmacol Ther 1997; 11:547–552.

70. Cremonini F, Nicandro JP, Atkinson V, et al. Randomised clinical trial: alosetron improves quality of life and reduces restriction of daily activities in women with severe diarrhoea-predominant IBS. Aliment Pharmacol Ther 2012;36:437–448.

71. Spiegel B, Camilleri M, Bolus R, et al. Psychometric evaluation of patient-reported outcomes in irritable bowel syndrome randomized controlled trials: a Rome Foundation report. Gastroenterology 2009;137:1944–1953. e1–3.

72. Tack J, Fried M, Houghton LA, et al. Systematic review: the efficacy of treatments for irritable bowel syndrome—a European perspective. Aliment Pharmacol Ther 2006;24:183–205.

73. Valenzuela J, Alvarado J, Cohen H, et al. [Latin-American consensus document on irritable bowel syndrome]. Gastroenterol Hepatol 2004;27:325–343.

74. Ford AC, Brandt LJ, Young C, et al. Efficacy of 5-HT3 antagonists and 5-HT4 agonists in irritable bowel syndrome: systematic review and meta-analysis. Am J Gastroenterol 2009;104:1831–1843; quiz 1844.

75. Cremonini F, Delgado-Aros S, Camilleri M. Efficacy of alosetron in irritable bowel syndrome: a meta-analysis of randomized controlled trials. Neurogastroenterol Motil 2003;15:79–86.

76. Spiller R, Aziz Q, Creed F, et al. Guidelines on the irritable bowel syndrome: mechanisms and practical management. Gut 2007;56:1770–1798.

77. Andresen V, Montori VM, Keller J, et al. Effects of 5-hydroxytryptamine (serotonin) type 3 antagonists on

symptom relief and constipation in nonconstipated irritable bowel syndrome: a systematic review and meta-analysis of randomized controlled trials. Clin Gastroenterol Hepatol 2008;6:545–555.

78. Lavo B, Stenstam M, Nielsen AL. Loperamide in treatment of irritable bowel syndrome—a double-blind placebo controlled study. Scand J Gastroenterol Suppl 1987;130:77–80.

79. Hovdenak N. Loperamide treatment of the irritable bowel syndrome. Scand J Gastroenterol Suppl 1987;130:81–84.

80. Ruepert L, Quartero AO, de Wit NJ, et al. Bulking agents, antispasmodics and antidepressants for the treatment of irritable bowel syndrome. Cochrane Database Syst Rev 2011:CD003460.

81. Bergmann M HA, Schlosser T. Therapy of irritable colon with trimipramine (Herphonal)—a controlled clinical study [Die therapie des colon irritabile mit trimipramin (Herphanol) - Eine kontrollierte studie]. Z Klin Med 1991;46:1621–1628.

82. Boerner D, Eberhardt R, Metz K, et al. Wirksamkeit ind vertraeglickkeit eines antidepressivums beim colon irritablie. Therapiewoche 1988;38:201–208.

83. Drossman DA, Toner BB, Whitehead WE, et al. Cognitive-behavioral therapy versus education and desipramine versus placebo for moderate to severe functional bowel disorders. Gastroenterology 2003;125:19–31.

84. Myren J, Groth H, Larssen SE, et al. The effect of trimipramine in patients with the irritable bowel syndrome. A double-blind study. Scand J Gastroenterol 1982;17:871–875.

85. Nigam P, Kapoor KK, Rastog CK, et al. Different therapeutic regimens in irritable bowel syndrome. J Assoc Physicians India 1984;32:1041–1044.

86. Talley NJ, Kellow JE, Boyce P, et al. Antidepressant therapy (imipramine and citalopram) for irritable bowel syndrome: a double-blind, randomized, placebo-controlled trial. Dig Dis Sci 2008;53:108–115.

87. Vahedi H, Merat S, Momtahen S, et al. Clinical trial: the effect of amitriptyline in patients with diarrhoea-predominant irritable bowel syndrome. Aliment Pharmacol Ther 2008;27:678–684.

88. Vij JG, Jiloha RC, Kumar N. Effect of antidepressant drug (doxepin) on irritable bowel syndrome patients. Indian J Psychiatry 1991;33:243–246.

89. Heefner JD, Wilder RM, Wilson ID. Irritable colon and depression. Psychosomatics 1978;19:540–547.

90. Furukawa T, McGuire H, Barbui C. Low dosage tricyclic antidepressants for depression. Cochrane Database Syst Rev 2003:CD003197.

91. Ford AC, Talley NJ, Schoenfeld PS, et al. Efficacy of antidepressants and psychological therapies in irritable bowel syndrome: systematic review and meta-analysis. Gut 2009;58:367–378.

92. Grover M, Drossman DA. Psychotropic agents in functional gastrointestinal disorders. Curr Opin Pharmacol 2008;8:715–723.

93. Kuiken SD, Tytgat GN, Boeckxstaens GE. The selective serotonin reuptake inhibitor fluoxetine does not change rectal sensitivity and symptoms in patients with irritable bowel syndrome: a double blind, randomized, placebo-controlled study. Clin Gastroenterol Hepatol 2003;1:219–228.

94. Ladabaum U, Sharabidze A, Levin TR, et al. Citalopram provides little or no benefit in nondepressed patients with irritable bowel syndrome. Clin Gastroenterol Hepatol 2010;8:42–48.e1.

95. Masand PS, Pae CU, Krulewicz S, et al. A double-blind, randomized, placebo-controlled trial of paroxetine controlled-release in irritable bowel syndrome. Psychosomatics 2009;50:78–86.

96. Tabas G, Beaves M, Wang J, et al. Paroxetine to treat irritable bowel syndrome not responding to high-fiber diet: a double-blind, placebo-controlled trial. Am J Gastroenterol 2004;99:914–920.

97. Tack J, Broekaert D, Fischler B, et al. A controlled crossover study of the selective serotonin reuptake inhibitor citalopram in irritable bowel syndrome. Gut 2006;55:1095–1103.

98. Khalif IL, Quigley EM, Makarchuk PA, et al. Interactions between symptoms and motor and visceral sensory responses of irritable bowel syndrome patients to spasmolytics (antispasmodics). J Gastrointestin Liver Dis 2009;18:17–22.

99. Su AM, Shih W, Presson AP, et al. Characterization of symptoms in irritable bowel syndrome with mixed bowel habit pattern. Neurogastroenterol Motil 2014;26:36–45.

Supplementary Methods

Search Strategies

Main search. Databases searched were OVID MED-LINE, OVID In-Process and Other Non-Indexed Citations, OVID EMBASE, Centre for Reviews and Dissemination, Wiley Cochrane, Health Technology Assessment, and NHS Economic Evaluation. Only the database searches for 5 therapies appear in the following text; the same combinations of text words and subject headings were used to search the other therapies.

1 exp Irritable Bowel Syndrome/ use acp,cctr, coch,clcmr,dare,clhta,cleed,mesz (4454)

2 exp Irritable Colon/ use emez (14269)

3 (Irritable colon or irritable bowel or functional bowel or spastic colon or ibs).ti,ab.

4 or/1–3 (24777)

5 exp Peptides/ use acp,cctr,coch,clcmr,dare,clhta, cleed,mesz (2262137)

6 exp linaclotide/ use emez (228)

7 (Linzess or constella or linaclotide).mp. (350)

8 (851199-59-2 or 851199-60-5).rn.(163)

9 exp Alprostadil/ use acp,cctr,coch,clcmr,dare,clhta, cleed,mesz (7231)

10 exp lubiprostone/ use emez (523)

11 (Amitiza or amitizia or lubiproston*).mp.(773)

12 136790-76-6.rn.(461)

13 exp Rifamycins/ use acp,cctr,coch,clcmr,dare,clhta, cleed,mesz(18513)

14 exp rifaximin/ use emez (2130)

15 (Rifaximin or lumenax or Xifaxan or Xifaxanta or Normix or Rifamycins).mp.(4965)

16 (80621-81-4 or 88747-56-2).rn.(2370)

17 exp Carbolines/ use acp,cctr,coch,clcmr,dare, clhta,cleed,mesz (5284)

18 exp Alosetron/ use emez (1144)

19 (Alosetron or liminos or lotronex).mp.(1533)

20 122852-42-0.rn.(1117)

21 or/5-20 (2293938

22 4 and 21 (2615)

23 (Meta Analysis or Controlled Clinical Trial or Randomized Controlled Trial).pt.(907382)

24 Meta-Analysis/ use mesz,acp,cctr,coch,clcmr,dare, clhta,cleed or exp Technology Assessment, Biomedical/ use mesz,acp,cctr,coch,clcmr,dare,clhta,cleed (54711)

25 Meta Analysis/ use emez or Biomedical Technology Assessment/ use emez (83518)

26 (meta analy* or metaanaly* or pooled analysis or (systematic* adj2 review*) or published studies or published literature or medline or embase or data synthesis or data extraction or cochrane or ((health technolog* or biomedical technolog*) adj2 assess*)).ti,ab.(372450)

27 exp Random Allocation/ use mesz,acp,cctr,coch, clcmr,dare,clhta,cleed or exp Double-Blind Method/ use mesz,acp,cctr,coch,clcmr,dare,clhta,cleed or exp Control Groups/ use mesz,acp,cctr,coch,clcmr,dare, clhta,cleed or exp Placebos/ use mesz,acp,cctr, coch,clcmr,dare,clhta,cleed (343621)

28 Randomized Controlled Trial/ use emez or exp Randomization/ use emez or exp RANDOM SAMPLE/ use emez or Double Blind Procedure/ use emez or exp Triple Blind Procedure/ use emez or exp Control Group/ use emez or exp PLACEBO/ use emez (621198)

29 (random* or RCT or placebo* or sham* or (control* adj2 clinical trial*)).ti,ab.(2168561)

30 or/23-29 (3005647)

31 22 and 30 (954)

32 limit 31 to english language [Limit not valid in CDSR,ACP Journal Club,DARE,CCTR,CLCMR; records were retained](905)

33 limit 32 to yr="1995 -Current" [Limit not valid in DARE; records were retained] (885)

34 remove duplicates from 33 (660)

Additional searches (limited to meta-analyses and technology assessments from 2004 onward). Databases searched were OVID MEDLINE, OVID In-Process and Other Non-Indexed Citations, OVID EMBASE, Centre for Reviews and Dissemination, Wiley Cochrane, and Health Technology Assessment. Only the database search for one therapy is shown; the same combinations of text words and search headings were used to search the other therapies.

1 exp Irritable Bowel Syndrome/ use coch,clhta,mesz (4170)

2 exp Irritable Colon/ use emez (15369)

3 (Irritable colon or irritable bowel or functional bowel or spastic colon or ibs).ti,ab. (24994)

4 or/1–3 (29722)

5 exp Carbolines/ use coch,clhta,mesz (5126)

6 exp Alosetron/ use emez (1173)

7 (Alosetron or liminos or lotronex).ti,ab. (561)

8 5 or 6 or 7 (6409)

9 Meta Analysis.pt. (47281)

10 Meta-Analysis/ use coch,clhta,mesz or exp Technology Assessment, Biomedical/ use coch,clhta,mesz (56626)

11 Meta Analysis/ use emez or Biomedical Technology Assessment/ use emez (89145)

12 (meta analy* or metaanaly* or pooled analysis or (systematic* adj2 review*) or published studies or published literature or medline or embase or data synthesis or data extraction or cochrane or ((health technolog* or biomedical technolog*) adj2 assess*)).ti,ab. (372553)

13 or/9–12 (421856)

14 4 and 8 and 13 (117)

15 limit 14 to yr="2004–Current" (83)

Glossary of Terms

Baseline risk is a synonym of "control event rate" or "control group risk." It is the observed risk of the event in the control group.

Estimate of effect is the observed relationship between an intervention and an outcome expressed as, for example, a number needed to treat, odds ratio, risk difference, risk ratio, relative risk reduction, standardized mean difference, or weighted mean difference.

Evidence profile contains detailed information about the quality of evidence and the summary of findings for each of the included outcomes. A GRADE evidence profile allows presentation of key information about all relevant outcomes for a given health care question. It presents information about the body of evidence (eg, number of studies), the judgments about the underlying quality of evidence, key statistical results, and a grade for the quality of evidence for each outcome.

Fragility refers to the effect a few events may have on a seemingly robust confidence interval. Changing a small number of events can lead to loss of statistical significance.

Inconsistency refers to heterogeneity or widely differing estimates of the treatment effect. When heterogeneity exists but no plausible explanation can be identified, one may consider downgrading the quality of the evidence.

Indirectness refers to differences between the question being addressed and the available evidence regarding the population, intervention, comparator, or outcome. The lack of direct (head-to-head) comparisons of 2 interventions is an additional source of indirectness.

Imprecision refers to wide confidence intervals around the estimate of effect often attributable to few events or relatively few patients.

Limitations of study design include lack of allocation concealment, lack of blinding (particularly if outcomes are subjective and their assessment is highly susceptible to bias), large loss to follow-up, and failure to adhere to an analysis according to intention-to-treat principle.

PICO shows that every health care management question has 4 components: Patients (population); Interventions (therapeutic, diagnostic, and so on.) under investigation (the experimental intervention, or in observational studies this may be exposure), Comparison (alternative intervention; intervention in the control group), Outcomes of interest.

Publication bias is a systematic underestimate or overestimate of the underlying beneficial or harmful effect due to the selective publication of studies (publication bias). Investigators may fail to report studies they have undertaken (typically those that show no effect) or journals may not accept studies that show no effect for publication.

Quality of evidence reflects the extent to which our confidence in an estimate of the effect is adequate to support a particular recommendation. In the GRADE approach to quality of evidence, randomized trials without important limitations provide high-quality evidence and observational studies without special strengths or important limitations provide low-quality evidence. Limitations or special strengths (ie, criteria for rating down or rating up) can, however, modify the quality of the evidence of both randomized trials and observational studies.

Rating down the quality of the evidence for an outcome: criteria/explanations for rating down include (1) limitations in study design, (2) inconsistency, (3) indirectness, (4) imprecision, and (5) publication bias.

Rating up the quality of the evidence for an outcome: criteria/explanations for rating down include (1) large or very large effect, (2) all plausible confounding from observational studies or randomized trials may be working to reduce the demonstrated effect, and (3) presence of a dose-response relation. Only studies with no threats to validity (not downgraded for any reason) may be upgraded.

Relative risk is a synonym of risk ratio. In intervention studies, it is the ratio of the risk in the intervention group to the risk in the control group. A risk ratio of 1 indicates no difference between comparison groups. For undesirable outcomes, a risk ratio that is <1 indicates that the intervention was effective in reducing the risk of that outcome.

Relative risk reduction is the proportional reduction in risk in one treatment group compared with another. It is 1 minus the risk ratio. If the risk ratio is 0.25, then the relative risk reduction is $1 - 0.25 = 0.75$ (or 75%).