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American College of Gastroenterology's Monograph on the Management of Irritable Bowel Syndrome

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Introduction

Irritable bowel syndrome (IBS) is the most prevalent of the functional gastrointestinal disorders (FGIDs). Current estimates are that IBS affects up to 10-12% of adults in North America (1, 2). Although it can affect all individuals regardless of age, creed, or gender, IBS is more common among women and is most commonly diagnosed in younger individuals (< age 50) (2, 3). IBS is characterized by recurrent abdominal pain and altered bowel habits; bloating and distention frequently coexist. The diagnosis of IBS is made by taking a careful history, eliciting key symptoms, as well as performing a physical examination and limited diagnostic testing (4-6). IBS is categorized into four main subtypes based on the predominant bowel habit: IBS with constipation (IBC-C); IBS with diarrhea (IBS-D); IBS with mixed symptomology (IBS-M); and unclassified IBS (5).

IBS imposes a significant burden to the health care system and to individuals. Direct medical costs attributed to IBS in the US, excluding prescription and over-the-counter medicines, were estimated at $1.5–$10 billion per year in 2005 (7). Patients with IBS enrolled in a large Health Maintenance Organization (HMO) had significantly more outpatient visits and incurred nearly 50% more in total costs than individuals without IBS (8). A retrospective case-control study from another large HMO reported that patients with IBS had significantly more diagnostic tests, imaging, and surgery compared with patients without a diagnosis of IBS (9). Significant variations in care across the United States related to the diagnosis and treatment of IBS also play a role in excessive health care costs (10). The burden of IBS on individuals can be measured in a number of ways. Studies have demonstrated consistently that IBS impairs work-related activities (e.g., lost work time, reduced productivity while at work) and also reduces quality of life (11, 12). The development

of effective and efficient treatment strategies for IBS assumes considerable importance, therefore, not just for the individual sufferer, but for society at large.

Given the clinical heterogeneity that is a hallmark of the disorder and the absence of a single effective therapy for all sufferers, available therapies tend to focus on predominant symptomatology at presentation (i.e., altered bowel habits, abdominal pain, or bloating) (4-6). Based on their purported mode of action, many pharmacological therapies for IBS developed in recent decades have been directed towards those with a particular bowel habit, whether diarrhea or constipation. However, treating IBS patients can be difficult as no validated treatment algorithm exists, not all patients respond to treatment, and patients with similar symptoms frequently respond to the same treatment differently. Fortunately, a variety of novel therapeutic strategies are being explored and new compounds have appeared since the last iteration of the ACG monograph on IBS (4). The goal of this document, therefore, is to provide an updated, evidence-based document on the therapy of this common and, at times, debilitating disorder.

An Overview of Methodology for Systematic Reviews of IBS Therapy

Prior to the last evidence-based systematic review on the management of irritable bowel syndrome commissioned and published by the ACG in 2014 (4), and the work that underpinned this, there had been several systematic reviews of available therapies for IBS (13-22). We have previously shown that these had either not synthesized the data correctly, or contained inaccuracies in applying eligibility criteria and data extraction (23). We have, therefore, updated all the rigorously performed

meta-analyses (24-27), which informed the ACG position statement in 2014, according to the following protocol:

Objectives

Primary Outcome

To assess the efficacy of available pharmacological therapies in treating IBS compared with placebo, or, in the case of psychological and dietary therapies, in comparison with either no treatment or standard/usual care.

Secondary Outcomes

To assess the efficacy of available pharmacological, psychological, and dietary therapies in treating IBS according to predominant stool pattern reported (IBS-C, IBS-D, or IBS-M), and to assess adverse events with pharmacological and other therapies for IBS.

Criteria for Considering Studies for this Review

Types of Studies

Only parallel-group randomized controlled trials (RCTs) comparing pharmacological therapies with placebo, or comparing psychological and dietary therapies with either no treatment or standard/usual care, were considered for this

review. Cross-over trials were eligible for inclusion, provided extractable data were provided at the end of the first treatment period, prior to cross-over.

Types of Participants

Adults over 16 years of age recruited from primary, secondary, or tertiary care with IBS symptoms diagnosed by any criteria (including clinical impression).

Types of Interventions

The following treatments were considered eligible:

1. Exercise, diet, and dietary manipulation
2. Fiber
3. Interventions that modify the microbiota: prebiotics, synbiotics, probiotics, and antibiotics
4. Antispasmodics and peppermint oil
5. Antidepressants
6. Psychological interventions
7. Pro-secretory agents: linaclotide, plecanatide, and lubiprostone,
8. Eluxadoline
9. Loperamide
10. Serotonergic agents
11. Polyethylene glycol
12. 5-aminosalicylates

Types of Outcome Measures

Subjects needed to be followed up for at least 1 week. The trials needed to include one or more of the following outcome measures:

1. Global assessment of IBS cure or improvement
2. Abdominal pain cure or improvement
3. Global IBS symptom or abdominal pain scores

Search Strategy for Identification of Studies

MEDLINE (1946 to July 2017), EMBASE and EMBASE Classic (1947 to July 2017), PsychINFO (1806 to July 2017), and the Cochrane central register of controlled trials were searched. The search strategy is given below:

Studies on IBS were identified with the terms irritable bowel syndrome and functional diseases, colon (both as medical subject heading (MeSH) and free text terms), and IBS, spastic colon, irritable colon, and functional adj5 bowel (as free text terms).

For RCTs of dietary manipulation these were combined using the set operator AND with studies identified with the terms: diet, fat-restricted, diet, protein-restricted, diet, carbohydrate-restricted, diet, gluten-free, diet, macrobiotic, diet, vegetarian, diet, Mediterranean, diet fads, gluten, lactose intolerance, or lactose (both as MeSH terms and free text terms), or the following free text terms: FODMAP$, glutens, or food adj5 intolerance.

For RCTs of fiber, antispasmodics, and peppermint oil these were combined using the set operator AND with studies identified with the terms: dietary fibre,

cereals, psyllium, sterculia, karaya gum, parasympatholytics, scopolamine, trimebutine, muscarinic antagonists, or butylscopolammonium bromide (both as MeSH and free text terms), or the following free text terms: bulking agent, psyllium fibre, fibre, husk, bran, ispaghula, wheat bran, spasmolytics, spasmolytic agents, antispasmodics, mebeverine, alverine, pinaverium bromide, otilonium bromide, cimetropium bromide, hyoscine butyl bromide, butylscopolamine, drotaverine, peppermint oil, or colpermin.

For RCTs of prebiotics, synbiotics, probiotics, and antibiotics these were combined using the set operator AND with studies identified with the terms: Saccharomyces, Lactobacillus, Bifidobacterium, Escherichia coli, probiotics, prebiotics, synbiotics, anti-bacterial agents, penicillins, cephalosporins, rifamycins, quinolones, nitroimidazoles, tetracycline, doxycycline, amoxicillin, ciprofloxacin, metronidazole, or tinidazole (both as MeSH and free text terms), or the following free text terms: antibiotic, or rifaximin.

For RCTs of antidepressants and psychological therapies, including hypnotherapy, these were combined using the set operator AND with studies identified with the terms: psychotropic drugs, antidepressive agents, antidepressive agents (tricyclic), desipramine, imipramine, trimipramine, doxepin, dothiepin, nortriptyline, amitriptyline, selective serotonin re-uptake inhibitors, paroxetine, sertraline, fluoxetine, citalopram, venlafaxine, cognitive therapy, psychotherapy, behaviour therapy, relaxation techniques, or hypnosis (both as MeSH terms and free text terms), or the following free text terms: behavioural therapy, relaxation therapy, or hypnotherapy.

For RCTs of linaclotide, plecanatide, lubiprostone, eluxadoline, and loperamide these were combined using the set operator AND with studies identified with the terms loperamide or antidiarrheals (both as MeSH and free text terms), as well as the following free text terms: linaclotide, constella, plecanatide, lubiprostone, amitiza, eluxadoline, viberzi, imodium, or lopex.

For RCTs of serotonergic agents these were combined using the set operator AND with studies identified with the terms: serotonin antagonists or receptors (serotonin, 5-HT_3) (both as MeSH and free text terms), or the following free text terms: 5-HT_3 or alosetron.

For RCTs of polyethylene glycol these were combined using the set operator AND with studies identified with the term polyethylene glycol (both as a MeSH and free text term).

For RCTs of 5-aminosalicylates these were combined using the set operator AND with studies identified with the following terms: sulfasalazine, mesalamine, or aminosalicylic acid (both as MeSH terms and free text terms), or the following free text terms: balsalazide, olsalazine, mesalazine, pentasa, asulfidine$, azulfadine$, azulfidine$, sulfasalazine$, salazopyrin$, salazosulfapyridine, 5-ASA, 5ASA, 5-aminosalicylic$, 5-aminosalicylate$, 5aminosalicylic$, or 5aminosalicylate$.

The search was limited to humans. No restrictions were applied with regard to language of publication. A recursive search of the bibliography of relevant articles was also conducted.

Abstracts

ACG, DDW, and UEGW abstract books between 2000 and 2016 were hand-searched. Authors of trial reports published only as abstracts were contacted and asked to contribute full datasets or completed papers.

Correspondence

Experts in the field were contacted for leads on unpublished studies.

Methods of the Review

Selection of Studies

The lead reviewer screened titles and trial abstracts that had been identified by the search strategy for articles that could possibly be eligible for the review. The lead reviewer then screened the selected trials to confirm eligibility, using pre-designed eligibility forms. A second reviewer, masked to the initial assessment, also evaluated all identified trials for eligibility. Discrepancies were resolved by discussion and a consensus view was taken.

Assessment of Study Quality

Only trials that used the word 'random’, ‘randomly’, or ‘randomized' in the description of their methodology were considered in this review and assessed for quality according to four characteristics:

a) Method used to generate the randomization schedule (truly random or not stated/unclear).

   Computer generated random numbers, coin toss, or card shuffles, etc. were defined as truly random.

b) Method used to conceal treatment allocation (adequate, inadequate, or unclear).

   If investigators were unaware of each participant's allocation to a treatment when they were recruited, then the allocation was said to be adequately concealed. Methods such as central randomization systems, or serially numbered opaque envelopes, fit these criteria.

c) Implementation of masking (patients masked, clinicians masked, outcome assessors masked).

   When an identical placebo was used it was assumed that the participants were masked to their treatment allocation.

d) Completeness of follow-up and intention-to-treat analysis.

   Wherever possible, completeness of follow-up and intention-to-treat analysis was recorded, as were dropout rates by group.

Study quality was assessed by one reviewer and checked by a second.

Data Extraction

All data were extracted independently by two investigators on to a Microsoft Excel spreadsheet (XP professional edition; Microsoft Corp, Redmond, WA, USA).

Any disagreement between investigators was resolved by discussion. The following characteristics were recorded for each trial:

- Setting: population-based, primary care, secondary care, tertiary care

- Country of origin and number of centers involved

- Dose of therapy

- Duration of therapy

- Adverse events: both total number and individual adverse events, if available

- Definition of IBS used

- Primary outcome measure used

Data were extracted as intention-to-treat analyses, with all drop-outs assumed to be treatment failures, wherever trial reporting allowed this.

Data Synthesis and Analysis

For binary outcomes, (global IBS symptoms or abdominal pain improved or cured), the impact of interventions were expressed as relative risks (RR) of global IBS symptoms or abdominal pain not improving, together with 95% confidence intervals (CIs). Data were pooled using a random effects model, in order to give a more conservative estimate of the efficacy of individual IBS therapies (28). The number needed to treat (NNT) for treatment efficacy, and the number needed to harm (NNH) for adverse events, were calculated using the formula NNT or NNH = 1 / (control event rate x (1 – RR)). These provide useful summary estimates for efficacy and

safety for each of the active interventions of interest over a placebo or control intervention, corresponding to the number of extra patients needing to be treated with the active intervention over and above placebo or the control intervention to see one of the events of interest (i.e. a patient experiencing an improvement of symptoms or an adverse event). However, it should be pointed out that these cannot be used to compare the relative efficacy of one active intervention versus another, as they are not based on head-to-head studies. In addition, for NNHs, which are derived from summaries of adverse events it is important to point out that the definitions of these adverse events are also not standardized between individual trials, so again should not be compared. For continuous data, such as global IBS symptom scores or individual IBS symptom scores, a standardized mean difference (SMD), with 95% CIs, was calculated.

The results of individual studies can be diverse, and this inconsistency within a single meta-analysis can be quantified with a statistical test of heterogeneity, to assess whether the variation across trials is due to true heterogeneity, or chance. This quantity is termed I^2, and its value ranges from 0% to 100%, with 0% representing no observed heterogeneity, and larger values indicating increasing heterogeneity. A value $\leq$50%, accompanied by a P value of > 0.10 for the χ^2 test, was arbitrarily chosen to represent low levels of heterogeneity (29).

Review Manager version 5.3.5 (RevMan for Windows 2014, The Nordic Cochrane Centre, Copenhagen, Denmark) was used to generate Forest plots of pooled RRs and SMDs for primary and secondary outcomes with 95% CIs, as well as funnel plots. The latter were assessed for evidence of asymmetry, and therefore possible publication bias or other small study effects, using the Egger test (30), if there were

sufficient (10 or more) eligible studies included in the meta-analysis, in line with published recommendations (31). GRADEpro version 3.6 (GRADE working group 2004-2007) was used to grade the quality of the evidence. Consensus was reached using a consensus-oriented decision-making framework (32), culminating in a face-to-face meeting to discuss the evidence and reach a unanimous decision on the quality of evidence and strength of recommendation.

1. Exercise, Diet and Dietary Manipulation

a. Exercise

We suggest exercise for overall symptom improvement in IBS patients

Recommendation: Weak

Quality of Evidence: Very low

Exercise and physical fitness are key elements of maintaining physical and mental health (33, 34). Studies from healthy volunteers and patients suggest that physical activity protects against gastrointestinal (GI) symptoms (35, 36), and bears an inverse relationship with colonic transit time (37).

Based upon these observations, it is reasonable to hypothesize that exercise might be beneficial to patients with IBS. To date, there have been few RCTs that have rigorously evaluated the benefits of exercise in IBS patients. Daley et al. invited 305 IBS patients to participate in a RCT that compared 12 weeks of an exercise intervention with usual care (38). Fifty-six IBS patients (18%) agreed to participate. Quality of life (IBS-QOL) and IBS symptoms (Birmingham IBS symptoms questionnaire) were assessed before and after the interventions. Exercise led to statistically significant benefits for constipation (95% CI: -1.6 to -20.1) but not for other outcomes such as abdominal pain, diarrhea, total symptom score, or quality of life.

In a second trial, Johannesson et al. randomized 102 IBS patients to a rigorous exercise program monitored by a physiotherapist or usual care for 12 weeks (39). Seventy-five IBS patients completed the trial. IBS symptom severity scores improved to a greater degree in the exercise arm compared with the control arm (P = 0.003).

The same authors reported long-term follow-up data (median follow-up 5.2 years) for 39 of the originally enrolled IBS patients (40). Increases in physical activity and improvements in symptom scores compared with baseline were maintained at follow-up.

Summary:

Although it is clear that exercise offers general health benefits and, whenever possible, should be encouraged the Task Force did not feel that the weight or strength of available evidence justified a strong recommendation regarding exercise for IBS. Although encouraging, the Task Force feels that the current body of evidence should be viewed as hypothesis-generating, and in need of validation by methodologically rigorous, appropriately powered, RCTs.

b. Diet and dietary manipulation for IBS

We suggest a low FODMAP diet for overall symptom improvement in IBS patients

Recommendation: Weak

Quality of evidence: Very low

We suggest against a gluten-free or exclusion diet based upon antibody or leukocyte activation test for overall symptom improvement in IBS patients

Recommendation: Weak

Quality of evidence: Very low

The majority of IBS patients associate symptom onset or worsening with eating a meal. Although true food allergy is uncommon in IBS patients, perceived

food intolerances or sensitivities are quite common. Up to 90% of IBS patients exclude certain foods in the hopes of avoiding or improving their GI symptoms (41).

Since the publication of the last IBS Task Force evidence-based review in 2014 (4), there have been numerous studies that have evaluated dietary therapies in IBS patients (42). Although various diets have been suggested to benefit IBS patients, the largest body of evidence relates to two specific diets; a diet low in fermentable oligo-, di-, and mono-saccharides, and polyols (FODMAPs) and a gluten-free diet.

We identified seven eligible RCTs (evaluating 397 participants) that provided dichotomous outcomes for a low FODMAP diet versus an alternative diet (43-49). There was an overall effect of the low FODMAP diet in reducing IBS symptoms with a RR of remaining symptomatic on a low FODMAP diet of 0.69 (95% CI 0.54 to 0.88). The NNT was 5 (95% CI 3 to 11) (Table 1).

Similar to another recent systematic review (50), our analysis found that all trials were subject to high risk of bias. Overall, the quality of the evidence was graded as very low, which related to imprecision resulting from the relatively small number of patients included in the trials, significant heterogeneity, and issues around blinding.

Three trials in 271 IBS patients compared the low FODMAP diet with an alternative diet (43, 44, 47), two with usual diet (46, 48), and one with a high FODMAP diet (45). The three trials that had adequate concealment of allocation and an alternative dietary intervention in the control arm showed no statistically significant benefit of a low FODMAP diet (RR = 0.82; 95% CI = 0.66 to 1.02) with no heterogeneity between studies (43, 44, 47). The results of these trials are more difficult to interpret as they were not placebo-controlled, but rather, comparative effectiveness trials assessing two active dietary interventions. In each of these RCTs,

the low FODMAP diet led to adequate relief of IBS symptoms in roughly half of the patients.

None of the RCTs have evaluated the long-term efficacy of, or adherence to, a low FODMAP diet, or the personalized maintenance diet that is instituted after individual FODMAP reintroduction. Potential harms, which should be balanced with benefit, include impact on quality of life (e.g. social encounters) and effects on the colonic microbiome, which could exert negative effects on colonic health (45, 51-53).

We identified two eligible trials evaluating a gluten-free diet in 111 patients with IBS (54, 55). Both were re-challenge trials involving IBS patients that reported that their symptoms were controlled with a gluten-free diet, but in whom celiac disease had been rigorously excluded. Participants were then randomized to have this diet spiked with gluten or not. This design only indirectly addresses the research question, as withdrawing a significant food group from the diet and then introducing it may enhance the likelihood of a nocebo response. There was no statistically significant impact on IBS symptoms in the gluten challenge versus gluten-free diet (RR = 0.46; 95% CI 0.16 to 1.28) with significant heterogeneity between studies (I^2 = 86%, P = 0.008) (Table 1).

Another RCT evaluated 150 patients with IBS randomized to exclude all foods for which they had abnormal levels of IgG antibodies, or a sham diet where patients were asked to avoid a similar number of foods, but this was not based upon the IgG antibody test results (56). This trial had an unclear risk of bias. Participants were followed for 12 weeks and 18 (28%) of 65 in the active intervention arm noted a significant improvement in symptoms, compared with 11 (17%) of 66 in the sham diet

arm. This difference in response rates was not statistically significant (P = 0.14). The authors reported marginal statistical significance in those that adhered to their diet.

A more recent RCT utilized leukocyte activation testing to evaluate a true vs. sham elimination diet in 58 IBS patients (57). This study reported no difference in the proportion of patients with adequate relief of their IBS symptoms (P = 0.31) or quality of life (P = 0.92) after 4 weeks (secondary endpoints). However, there was a significantly greater increase in IBS global improvement scale score (primary endpoint) with the true vs. sham elimination diet (P = 0.04) after 4 weeks.

Summary:

Dietary therapies for IBS are of growing interest to patients, providers, and investigators. At present, the largest body of literature pertains to the low FODMAP diet. The available evidence supports a possible benefit for overall IBS symptoms in roughly half of sufferers. There are much less data for a gluten-free diet or elimination diets based upon IgG antibody or leukocyte activation testing. Importantly, there are little or no data that address the long-term efficacy, adherence, or harms of dietary therapies for IBS.

2. Fiber in IBS

We recommend fiber for overall symptom improvement in IBS patients

Recommendation: Strong.

Quality of evidence: Moderate.

We recommend psyllium, but not wheat bran, for overall symptom improvement in IBS patients

Recommendation: Strong.

Quality of evidence: Moderate

The updated systematic review and meta-analysis on fiber in IBS performed for this guideline identified 15 RCTs, involving 946 patients (58-72). Only one trial was at low risk of bias (70).

There was a statistically significant effect in favor of fiber compared with placebo (RR of IBS not improving = 0.87; 95% CI 0.80 to 0.94) (Table 1). There was no significant heterogeneity between results (I^2 = 0%, P = 0.53). Six studies used bran in a total of 411 patients (58, 59, 64, 65, 69, 70), seven studies ispaghula husk in a total of 499 patients (60-63, 66, 67, 70), and the remaining three studies used "concentrated fiber" (68), linseeds (71), or rice bran (72). Bran had no significant effect on treatment of IBS (RR of IBS not improving = 0.90; 95% CI 0.79 to 1.03), but ispaghula was effective in treating IBS (RR = 0.83; 95% CI 0.73 to 0.94). The NNT with ispaghula was 7 (95% CI 4 to 25).

Data on overall adverse events were only provided by seven trials (63, 64, 66, 68, 70-72). These trials evaluated 606 patients. A total of 130 (36.6%) of 355 patients receiving fiber reported adverse events, compared with 63 (25.1%) of 251 in the

placebo arms (RR = 1.06; 95% CI 0.92 to 1.22). There were insufficient data from individual studies to assess adverse events according to type of fiber administered.

Summary:

Poorly fermentable, soluble fiber remains an evidence-based treatment for IBS. Insoluble fiber may exacerbate pain and bloating in IBS, and has no evidence for efficacy. The low cost and lack of significant side effects makes soluble fiber a reasonable first-line therapy for IBS patients and, in combination with the moderate quality of evidence, is the basis of a strong recommendation. The ability to improve stool viscosity and frequency logically argues for the use of fiber in patients with IBS-C, although the evidence base to support this contention is far from conclusive.

3. Interventions that modify the microbiota: prebiotics, synbiotics, probiotics and antibiotics.

a. Prebiotics and synbiotics

We suggest against the use of prebiotics and synbiotics for overall symptom improvement in IBS patients

Recommendation: Weak

Quality of evidence: Very low

The concept that alterations in the gut microbiome might be relevant to IBS arose from observations that symptoms of IBS developed after an infection (post-infectious IBS) (73), that small intestinal bacterial overgrowth (SIBO) may cause symptoms indistinguishable from IBS (74), and that the colonic microbiota is altered

in IBS (75, 76). In addition, some IBS symptoms (e.g. bloating, slowed intestinal transit, and early satiety) have been associated with specific gut microbiota profiles (77, 78).

These observations have also led to the use of prebiotics, probiotics, and synbiotics, as well as antibiotics, in the treatment of IBS. Prebiotics are food or dietary supplements that result in specific changes in the composition and/or activity of the GI microbiota. Probiotics have been defined as "live microorganisms that, when administered in adequate amounts, confer a health benefit on the host" (79). Synbiotics, which are also food or dietary supplements, are a mixture of probiotics and prebiotics that act synergistically to promote the growth and survival of beneficial organisms.

The previous monograph identified no trials of prebiotics in IBS (4). The updated search identified one RCT (80). In this study 128 patients with IBS-D were recruited, and randomized to receive either prebiotics (derived from chicory) or placebo for 8 weeks. This double-blind trial was at unclear risk of bias due to failure to report the method used to conceal treatment allocation. Neither global IBS symptoms nor abdominal pain were reported as a dichotomous outcome by the investigators. Mean abdominal pain relief scores at 8 weeks were significantly higher with the prebiotic vs. the placebo (4.92±0.86 vs. 3.13±1.36, $P < 0.001$). Flatulence scores were also significantly improved with prebiotic (4.97 vs. 2.98, $P = 0.037$). Data on adverse events were incompletely reported.

With regards to synbiotics, no new RCTs were identified since the last version of the monograph (4), but there were two studies that recruited a total of 198 patients (81, 82). The first was a single-blind RCT conducted in Italy (81), recruiting 68

patients with IBS, and which used a combination of Lactobacillus acidophilus and helveticus, with Bifidobacterium species, in a vitamin and phytoextract-enriched medium for 12 weeks. Only this trial reported dichotomous data. There were 7 (20.6%) of 34 patients assigned to synbiotics with persistent symptoms, compared with 30 (88.2%) of 34 assigned to control therapy ($P < 0.01$). The second study, conducted in South Korea (82), used Bifidobacterium lactis in combination with acacia fiber for 8 weeks in 130 patients. This double-blind trial was at unclear risk of bias due to failure to report the method used to conceal treatment allocation. Both trials assessed IBS symptoms on a continuous scale in 185 patients. Even though both trials were individually positive, there was no statistically significant effect of synbiotics in reducing symptoms, due to significant heterogeneity between studies (SMD = -1.73; 95% CI -3.73 to 0.27, $I^2 = 96\%$, P = 0.09). In both synbiotic studies adverse events were reported, and no significant events occurred in either treatment arm.

b. Probiotics

We suggest probiotics, taken as a group, to improve global symptoms as well as bloating and flatulence in IBS patients

Recommendation: Weak

Quality of evidence: Low

Since the previous monograph a total of 18 new trials were identified (47, 83-99). Therefore, in total, there were 53 RCTs (47, 83-134), involving 5545 patients. Twenty-six trials were at low risk of bias, (47, 83, 84, 87-90, 92, 93, 96, 98, 99, 103,

105, 110, 112, 114, 115, 119, 121, 123, 124, 126, 130, 132, 133) with the remainder being unclear. There were 37 RCTs involving 4403 patients that gave outcomes as a dichotomous variable (47, 84, 86-89, 91, 92, 94-104, 110, 112, 113, 115, 118, 119, 121, 123, 125-134).

Probiotics were statistically superior to placebo (RR of IBS not improving = 0.81; 95% CI 0.74 to 0.88), with a NNT of 7 (95% CI 5 to 12) (Table 1). However, there was significant heterogeneity between studies (I^2 = 71%, P < 0.001), and evidence of funnel plot asymmetry or other small study effects (Egger test, P = 0.06). Combination probiotics were assessed in 21 RCTs, containing 1931 patients, with a benefit of probiotics compared with placebo (RR = 0.79; 95% CI 0.68 to 0.91), but with significant heterogeneity between studies (I^2 = 72%, P < 0.001), and there was evidence of publication bias or other small study effects (Egger test, P = 0.06).

Probiotics appeared to have beneficial effects on global IBS symptom scores or abdominal pain scores (SMD = -0.21; 95% CI -0.31 to -0.10), bloating scores, (SMD = -0.13; 95% CI -0.24 to -0.02), and flatulence scores (SMD = -0.23; 95% CI -0.38 to -0.08), although with significant heterogeneity in some of these analyses.

Total adverse events were reported by 36 RCTs (85-87, 89-93, 95-97, 99-106, 111, 113-116, 118-124, 127, 129, 130, 132, 133), containing 4183 patients. The RR of experiencing any adverse event was not significantly higher with probiotics (1.09; 95% CI 0.91 to 1.29).

c. Antibiotics

We suggest the non-absorbable antibiotic rifaximin for reduction in global IBS symptoms as well as bloating in non-constipated IBS patients

Recommendation: Weak

Quality of evidence: Moderate

We identified three additional RCTs of antibiotics in IBS (135-137) since the previous monograph (4), meaning there were a total of 9 RCTs reported in 8 papers (135-142). These trials involved 2845 participants. Overall, antibiotic therapy improved IBS symptoms compared with placebo (RR of symptoms not improving = 0.79; 95% CI 0.70 to 0.90), but with statistically significant heterogeneity between studies (I^2 = 75% P < 0.001). The NNT was 7 (95% CI 5 to 14.5).

Six RCTs used the minimally absorbed antibiotic rifaximin (137, 139-142), in patients representative of usual clinical practice, recruiting 2441 non-constipated IBS patients (predominantly IBS-D). Overall, there was a statistically significant benefit in favor of the antibiotic (RR = 0.86; 95% CI 0.81 to 0.91) with no significant heterogeneity noted between the studies (I^2 = 0%, P = 0.71) (Table 1). The NNT was 10.5 (95% CI 8 to 16). There was a seventh trial (136), recruiting 213 patients with IBS who also had lactose intolerance and bacterial overgrowth on breath testing. When this trial was included rifaximin remained an effective treatment (RR = 0.82; 95% CI 0.72 to 0.95), but with significant heterogeneity between studies (I^2 = 77%, P < 0.001). The NNT was 8 (95% CI 5 to 29). There were four rifaximin RCTs at low risk of bias, assessing 1966 patients (137, 139, 142), and pooled data from these four trial suggested rifaximin was superior to placebo in terms of improving IBS

symptoms (NNT = 11; 95% CI = 8 to 21). The quality of evidence was considered moderate due to the modest impact on IBS symptoms and heterogeneity between studies. A pooled analysis revealed no difference in adverse events (52% in both rifaximin and placebo arms) or serious adverse events (approximately 2% in each arm) between rifaximin and placebo (143).

There has been concern with antibiotic therapies for IBS due to the risk of developing Clostridium difficile infection. A pooled analysis of the phase 2b study and two of the phase 3 studies found C. difficile in one patient at study entry who subsequently was removed from the study (143). There was a zero incidence of C. difficile colitis that developed de novo. In the TARGET 3 trial, a further case of C. difficile colitis was reported among the 328 patients randomized to re-treatment with rifaximin (137).

In an effort to understand the mechanism of action of rifaximin, there have been additional concerns about the impact of this drug on the gut microbiota. Studies have revealed that a 2-week course of treatment causes modest, but detectable, changes in microbial profiles of the feces (144, 145). Other research studies evaluating fecal microbial profiles from IBS patients demonstrated that rifaximin effects on the microbiota were limited and not sustained (145-147).

Summary:

Despite the fact that patients and clinicians may use or recommend prebiotics or synbiotics, there are few data to support their use. Although overall there was a benefit of probiotics the evidence was low quality and hence they receive a weak recommendation. Variations in study design, IBS subtype recruited, type and dose of probiotic, as well as the small size of some of the study populations, and a lack of

comparative studies, preclude a recommendation on use of a particular species or strain for the treatment of IBS, or the subtype most likely to respond. Although rifaximin treatment appears to be beneficial in IBS, its efficacy is modest. The modest efficacy is why the Task Force gave a weak recommendation, despite the moderate quality data. Although data from preliminary studies concerning rates of C. difficile infection and microbial resistance are reassuring (143, 144, 148), future research should continue to examine these outcomes, particularly in patients receiving repeated courses of rifaximin. Advances in molecular techniques may provide further insight into the fecal microbiota of IBS patients compared with healthy controls, which may in turn improve the understanding of the role of antibiotic therapy, and its place in the treatment of this complex disorder.

4. Antispasmodics and Peppermint Oil in IBS

a. Antispasmodics

We suggest certain antispasmodics (otilonium, pinaverium, hyoscine, cimetropium, drotaverine, and dicyclomine) for overall symptom improvement in IBS patients

Recommendation: Weak

Quality of evidence: Very low

We identified three additional studies evaluating antispasmodics since the previous monograph (149-151). We therefore included 26 RCTs (60, 63, 64, 149-171), evaluating 2811 patients with IBS. Risk of bias was low in two of the trials (149, 150). Antispasmodic therapy had a statistically significant effect in improving IBS symptoms (RR of IBS symptoms not improving = 0.65; 95% CI 0.56 to 0.76). The NNT was 5 (95% CI 4 to 8) (Table 1). There was statistically significant heterogeneity (I^2 = 69%, P <0.001) and there were 13 different antispasmodics

evaluated. There was also funnel plot asymmetry (Egger test, P = 0.035), which may indicate publication bias or other small study effects, although this was difficult to interpret with so many different antispasmodics being studied.

The effect of individual antispasmodics was also difficult to interpret as there were only a small number of studies evaluating each drug. Otilonium was studied in five RCTs, including 791 patients (162, 163, 168, 169, 171), with a beneficial effect (RR = 0.70; 95% CI 0.54 to 0.90), and a NNT of 5 (95% CI 4 to 11), but borderline heterogeneity between study results (I^2 = 44%, P = 0.13). Pinaverium bromide was studied in four trials (150, 156-158), assessing 615 patients, and there was a statistically significant effect on improving IBS symptoms (RR = 0.56; 95% CI 0.38 to 0.82) with a NNT of 4 (95% CI 3 to 6). There was statistically significant heterogeneity (I^2 = 61%, P = 0.05). Hyoscine bromide was studied in three RCTs (60, 63, 152), assessing 426 patients, and there was a statistically significant effect on improving IBS symptoms (RR = 0.63; 95% CI 0.51 to 0.78) with a NNT of 3 (95% CI 2 to 25). There was no statistically significant heterogeneity in the results (I^2 = 0%, P = 0.62). Cimetropium bromide was studied in three trials (153-155), assessing 158 patients, and there was a statistically significant effect on improving IBS symptoms (RR = 0.38; 95% CI 0.20 to 0.71) with a NNT of 3 (95% CI 2 to 12.5). There was no statistically significant heterogeneity in the results (I^2 = 37%, P = 0.20). Drotaverine was studied in two RCTs (149, 151), containing 150 patients, and was more effective than placebo (RR = 0.31; 95% CI 0.19 to 0.50, NNT = 2 (95% CI 2 to 3), I^2 = 29%, P = 0.24). Finally, dicyclomine hydrochloride was studied in one trial (167), assessing 97 patients and there was a statistically significant effect on improving IBS symptoms (RR of IBS not improving = 0.65; 95% CI 0.45 to 0.95) with a NNT of 4 (95% CI 2 to 25). Mebeverine (one trial), trimebutine (three trials), pirenzipine (one trial), alverine

(one trial), rociverine (one trial), prifinium (one trial), and propinox (one trial) did not have a statistically significant effect on IBS symptoms, although the number of patients studied were small.

Seventeen trials reported adverse events with either active drug or placebo (64, 149-156, 159-161, 163, 165, 167, 168, 171). When data were pooled the incidence of adverse events was significantly higher among those taking antispasmodics, compared with placebo (RR = 1.60; 95% CI 1.15 to 2.21), with a NNH of 22 (95% CI 12 to 200). The commonest adverse events were dry mouth, dizziness, and blurred vision, but there were no serious adverse events reported in either treatment arm in any of the trials.

b. Peppermint oil

We suggest peppermint oil for overall symptom improvement in IBS patients

Recommendation: Weak.

Quality of evidence: Low

We identified two additional studies of peppermint oil since the previous monograph (172, 173). There were therefore seven RCTs (172-178), involving 634 patients. In one of these, there were no dichotomous data reported, but we contacted the authors and successfully obtained these (172). There were only two RCTs at low risk of bias (172, 178) There was a statistically significant effect in favor of peppermint oil compared with placebo (RR = 0.54; 95% CI 0.39 to 0.76). The NNT with peppermint oil was 4 (95% CI 3 to 6) (Table 1). However, there was significant heterogeneity between results (I^2 = 73%, P = 0.001). There were too few studies to assess for any evidence of funnel plot asymmetry.

Data on overall adverse events were provided by six trials (172, 173, 175-178). When data were pooled, the incidence of adverse events was not significantly higher among those taking peppermint oil, compared with placebo (RR = 1.90; 95% CI 0.81 to 4.48).

Summary:

Although anti-spasmodics have been a mainstay of IBS management for decades, based on the assumption that dysmotility or "spasm" may be fundamental to the pathogenesis of IBS symptoms, and of pain in particular (179), the evidence base to support their use remains modest. Most studies involving anti-spasmodics in IBS are small in size and were performed long before current standards for the definition of (5), and conduct of clinical trials in (180), FGIDs were developed. Nevertheless, antispasmodics, as a category, do appear to exert short-term benefits in IBS.

Our analysis suggests a benefit for peppermint oil in IBS, but this recommendation is based on a small number of clinical trials involving very specific formulations. Their findings should not be extrapolated to the many other products available through a variety of sources that have not been subjected to study. Although, overall, adverse events appeared to be no more common with peppermint oil than placebo, heartburn has been reported (181), presumably related to its effect as a relaxant of esophageal muscle. This could be an issue in an IBS subject, given the frequent occurrence of this symptom in the IBS sufferer (182), but may be avoided by the use of enteric coated preparations that provide more distal delivery.

5. Antidepressants for the treatment of IBS

We recommend TCAs for overall symptom improvement in IBS patients

Recommendation: Strong

Quality of evidence: High

We suggest SSRIs for overall symptom improvement in IBS patients

Recommendation: Weak

Quality of evidence: Low

Similar to other FGIDS, symptoms of IBS may arise as a manifestation of a brain-gut disorder (5, 6). Abnormalities in brain-gut function include disorders of sensory processing, leading to both visceral and central hypersensitivity (183). The high prevalence of overlapping psychological disorders in IBS patients, including anxiety, depression, and somatization (184, 185), has encouraged many providers to use centrally acting therapies, including neuromodulators and psychological therapies. The two classes of central neuromodulators most commonly used to treat FGIDs are tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs). As well as their effects on central pain and psychological distress, TCAs and SSRIs may also impact on bowel function, with TCAs improving diarrhea by slowing GI transit, and SSRIs ameliorating constipation by accelerating GI transit (186, 187).

We updated the previous version of the monograph (4), and identified one further paper (188). Overall, the search strategy identified a total of 18 RCTs (63, 188-204), evaluating 1127 patients. Only four of the RCTs were at low risk of bias (188, 194, 203, 204), with the remainder being unclear.

As a group, antidepressants (both TCAs and SSRIs) were found to be effective for treating IBS symptoms (RR of symptoms not improving with antidepressants = 0.66; 95% CI 0.57 to 0.76) (Table 1). Not unexpectedly, given differences in study design, heterogeneity was identified in these results, although this was of borderline statistical significance (I^2 = 37%; P = 0.06). A funnel plot analysis showed statistically significant asymmetry (Egger test, P = 0.03) suggesting possible publication bias or the influence of other small study effects. This asymmetry appeared to be overly influenced by the TCA arm of one small study (200); when this was removed from the analysis the asymmetry resolved. The NNT was 4 (95% CI 3.5 to 6). Seven RCTs reported effects of antidepressants on abdominal pain (189, 193, 195-198, 204). The RR of abdominal pain persisting was 0.62 (95% CI 0.43 to 0.88). However, significant heterogeneity was noted between studies (I^2 = 72%, P = 0.001).

TCAs were studied in 12 RCTs involving a total of 787 patients (63, 188-194, 197, 200, 201, 204). Patients treated with a TCA were more likely to report an improvement in IBS symptoms compared with those treated with placebo (RR = 0.65; 95% CI 0.55 to 0.77). No significant heterogeneity was noted between the studies (I^2 = 34%; P = 0.12). The NNT with TCAs was 4 (95% CI 3.5 to 7). Only three RCTs were low risk of bias (188, 194, 204), but when only these studies were included in the analysis the beneficial effect of TCAs in IBS remained (RR = 0.58; 95% CI 0.36 to 0.94, NNT = 5; 95% CI 2 to 24).

SSRIs were studied in seven RCTs involving a total of 356 patients (195, 196, 198-200, 202, 203). Patients treated with an SSRI were more likely to note a reduction in IBS symptoms compared with those treated with placebo (RR = 0.68; 95% CI 0.51 to 0.91). Significant heterogeneity was identified between individual trials (I^2 = 49%; P = 0.07). The NNT with SSRIs was 5 (95% CI 3 to 16.5).

Some of the strongest evidence for the pain-modifying effects of antidepressants in chronic painful disorders comes from high quality RCTs of the serotonin and norepinephrine re-uptake inhibitors (SNRIs) duloxetine and milnacipran, (205-209) neither of which have been tested in IBS trials to date. However, one open-label trial of duloxetine, which involved 13 patients with IBS and a generalized anxiety disorder, had encouraging results (210).

Overall adverse events, comparing either a TCA or SRRI to placebo, were reported in eight studies (188-191, 193, 195, 199, 201). The incidence of adverse events was higher in patients treated with an antidepressant compared with those treated with placebo (RR = 1.56; 95% CI 1.23 to 1.98). The NNH was 8.5 (95% CI 5 to 21). The most common adverse events reported in those taking a TCA were drowsiness and dry mouth.

Summary:

Both TCAs and SSRIs are effective in relieving pain and overall symptoms in IBS. These agents have both central and peripheral effects; their relative importance to efficacy in IBS is unclear. Whether all IBS sufferers, or only certain sub-populations, respond to anti-depressants is also unclear, and therapy with these agents may be limited by patient acceptance and adverse events, such as dry mouth.

6. Psychological Therapies

We suggest some psychological therapies (provider-directed cognitive behavioral therapy, relaxation therapy, hypnotherapy, and multicomponent psychological therapy) for overall symptom improvement in IBS patients

Recommendation: Weak

Quality of evidence: Very low

There were a total of 34 articles (194, 211-243), reporting on 36 separate RCTs, comparing various psychological therapies with control therapy in the form of symptom monitoring, physician's "usual management", supportive therapy, or placebo for the treatment of IBS in a total of 2487 patients. Four of these were identified since the previous monograph. (234, 238, 242, 243) None of the trials were considered to be at low risk of bias.

IBS patients treated with psychological therapies were more likely to improve than patients not treated with psychological intervention (RR = 0.69; 95% CI 0.62 to 0.76). The NNT was 4 (95% CI 3.5 to 5.5) (Table 1). However, there was significant heterogeneity between the studies (I^2 = 69%, P < 0.001), and funnel plot analysis demonstrated asymmetry (Egger test, P < 0.001), suggesting possible publication bias. Cognitive behavioral therapy, relaxation therapy, multi-component psychological therapy, hypnotherapy, and dynamic psychotherapy were all more effective than control therapy, when data from two or more RCTs were pooled, with NNTs of between 4 and 6. Multi-component psychological therapy delivered mainly via the telephone, contingency management, and emotional awareness and expression

training also appeared beneficial, although there was only one RCT for each of these treatment modalities. Finally, adverse events data were poorly reported among trials.

Summary:

Various psychological therapies appear to be effective in IBS but the interpretation of many studies is hampered by the absence of a true sham control which is, admittedly, difficult to construct for these particular interventions. Some benefits may also be therapist-dependent, and may not be reproducible when performed by a non-expert. These therapies may not be widely available and can be time consuming for the patient and the therapist; it is possible that, in the future, electronic technologies may improve access. They appear to be safe, although few RCTs report adverse events.

7. Prosecretory agents

a. Linaclotide

We recommend linaclotide for overall symptom improvement in IBS-C patients

Recommendation: Strong

Quality of evidence: High

Linaclotide is a 14-amino acid peptide, which is structurally related to human guanylin and uroguanylin. It is a truncated homolog of heat-stable enterotoxins (ST) from E. coli, which are natural ligands to the guanylate cyclase-C (GC-C) receptor, and its three disulfide bonds engender a high affinitiy for this receptor, irrespective of pH. Once bound to the GC-C receptor the drug activates the cystic fibrosis

transmembrane regulator, resulting in luminal chloride, bicarbonate, and water secretion. There is also evidence from animal studies that activation of GC-C leads to cyclic GMP release, which inhibits nociceptors, leading to improvements in abdominal pain (244).

Four RCTs of linaclotide were identified (245-248), one of which had been conducted since the last version of the monograph (245). In total, these trials recruited 2867 patients. All four trials were at low risk of bias. Summary results favored linaclotide, with a RR of 0.81 (95% CI 0.77 to 0.85), a NNT of 6 (95% CI 5 to 8), and no significant heterogeneity (I^2 = 0%, P = 0.42) (Table 1). All four trials also reported on abdominal pain improvement as an endpoint. Again, treatment effects favored linaclotide, with a RR of 0.82 (95% CI 0.75 to 0.89), and a NNT of 8 (95% CI 5 to 14).

Overall adverse events were provided by three trials (245, 247, 248), and were more frequent in the linaclotide arm (RR = 1.10; 95% CI 1.01 to 1.19). Individual adverse events were reported by all four trials (245-248). Diarrhea occurred more frequently in the linaclotide arm (RR = 6.81; 95% CI 4.69 to 9.90). The NNH was 7 (95% CI 6 to 11).

b. Plecanatide

We recommend plecanatide for overall symptom improvement in IBS-C patients

Recommendation: Strong

Quality of evidence: Moderate

Plecanatide is a 16-amino acid peptide similar to uroguanylin, a naturally occurring gut hormone, which also stimulates the enterocyte GC-C receptor but, unlike linaclotide, in a pH-dependent manner. Activation results in electrolyte and fluid transport into the lumen. The drug was initially approved by the Food and Drug Administration (FDA) for the treatment of chronic idiopathic constipation and, more recently, for IBS-C.

There are now published trial data available regarding its effect in patients with IBS-C. Three RCTs were identified, two phase 3 RCTs published in press in a single article (249), and one dose-ranging trial published in abstract form only (250), containing 2612 patients. The two phase 3 RCTs were considered low risk of bias (249). Pooled data suggests a positive effect of plecanatide on IBS symptoms (RR of remaining symptomatic = 0.88; 95% CI 0.84 to 0.92), with no significant heterogeneity, and a NNT of 10 (95% CI 8 to 14) (Table 1). The quality of evidence was considered moderate due to the modest impact on IBS symptoms.

Total adverse events data were not available for the three studies individually, but were pooled for the two phase 3 trials (249), with 23.8% of patients assigned to 3mg o.d. of plecanatide reporting any adverse event, 19.8% of those randomized to 6mg o.d. of plecanatide, and 18.6% of those allocated to placebo (249). Rates of diarrhea were reported separately for these two RCTs on the company's website (251,

252), and were higher with plecanatide, with a RR of 4.22 (95% CI 1.29 to 13.76). The NNH was 33 (95% CI 20 to 91). Of note, it is difficult to directly compare head-to-head NNH calculations between the two available GC-C agonists, as the definition of 'diarrhea' as an adverse event varies between the clinical trials of linclotide and plecanatide. Another recent meta-analysis examining this issue concluded that the numerically lower rates of diarrhea for plecanatide may be related to definitional variations among published trials (253).

c. Lubiprostone

We recommend lubiprostone for overall symptom improvement in IBS-C patients

Recommendation: Strong

Quality of evidence: Moderate

Lubiprostone is a molecule that activates the intestinal chloride channel type 2 on the apical surface of small intestinal enterocytes. Activation leads to a chloride and water efflux into the luminal cavity, which results in accelerated GI transit.

During this search, no new RCTs of lubiprostone in IBS patients were identified. As such, the assessment of findings and conclusions are unchanged from the previous monograph (4). Three trials were reported in two papers (254, 255), and all were at low risk of bias. Combined, lubiprostone was superior to placebo with a RR of 0.91 (95% CI 0.87 to 0.95) (Table 1). The NNT was 12.5 (95% CI 8 to 25). The quality of evidence was considered moderate due to the modest impact on IBS symptoms. There was no significant heterogeneity between trial results (I^2=0%, P = 0.92). Funnel plot asymmetry could not be assessed due to the low number of studies.

Adverse events were reported by 66% of patients receiving lubiprostone compared with 58% of patients on placebo (RR = 1.13; 95% CI 0.87 to 1.48). The only symptom occurring more frequently amongst those on active treatment was diarrhea (NNH=10; 95% CI 5 to 25). Nausea is well-described in patients taking lubiprostone (256), but only one RCT reported these data (255), and there was no significant difference in rates.

Summary:

The prosecretory agents linaclotide, plecanatide, and lubiprostone appear to improve symptoms among patients with IBS-C compared with placebo. For all three drugs, the most common side effect was diarrhea.

8. Eluxadoline

We suggest eluxadoline for overall symptom improvement in IBS-D patients

Recommendation: Weak

Quality of evidence: Moderate

Eluxadoline is a μ-opioid and κ-opioid receptor agonist and δ-opioid receptor antagonist in the enteric nervous system, and is FDA-approved for the management of IBS-D.

Three clinical trials, published in two papers (257, 258), and recruiting 3235 IBS-D patients were found. All three studies were low risk of bias. When data were pooled eluxadoline was superior to placebo (RR = 0.91; 95% CI 0.85 to 0.97) (Table 1). The NNT was 12.5 (95% CI 8 to 33). However, significant heterogeneity was

detected between studies (I^2 = 66%, P = 0.05). There was no clear effect on abdominal pain (RR = 0.95; 95% CI 0.89 to 1.02) but a statistically significant effect on stool consistency (RR = 0.88; 95% CI 0.80 to 0.96), with a NNT of 10 (95% CI 6 to 25). The quality of evidence was considered moderate due to the modest impact on IBS symptoms, and the unexplained heterogeneity between studies.

For the dose of 100mg twice daily, three trials reported improvement in IBS (RR of symptoms not improving = 0.90; 95% CI 0.86 to 0.95) with a NNT of 13 (95% CI 9 to 24). For the dose of 75mg twice daily, two trials reported improvement in IBS (RR of symptoms not improving = 0.92; 95% CI 0.87 to 0.97) with a NNT of 15 (95% CI 9 to 40).

Total adverse events from the three trials were reported, but were pooled for the two RCTs reported in a single paper (257). In the study by Dove et al. (258), overall adverse event rates were comparable in those receiving eluxadoline and placebo (48% v. 49%). However, four cases of pancreatitis were reported with eluxadoline. In the pooled data from the two phase III trials (257), again overall adverse event rates were comparable (59% vs. 56%). Symptoms more common in those receiving eluxadoline included constipation (8% vs. 2.5), nausea (8% vs. 5%), and vomiting (4% vs. 1%). Five cases of pancreatitis were reported with eluxadoline, along with eight cases of sphincter of Oddi spasm.

Summary:

Eluxadoline appears to help global symptoms and stool consistency in patients with IBS-D. Because of the risk of pancreatitis, eluxadoline should not be used in patients in whom their gallbladder has been removed or who have a history of sphincter of Oddi problems, pancreatitis, alcohol abuse, alcohol addiction, drink more

than 3 alcoholic drinks a day, or have severe liver problems. Accordingly, the Task Force gave a weak recommendation, despite high quality evidence, due to the fact that the medication may have serious side effects, together with the modest efficacy.

9. Loperamide

We suggest against loperamide for overall symptom improvement in IBS patients

Recommendation: Strong

Quality of evidence: Very low

There were no new RCTs of loperamide identified, so we included two trials involving 42 patients (259, 260). There was no statistically significant effect of loperamide compared with placebo (RR = 0.42; 95% CI 0.14 to 1.42) (Table 1). Both trials stated the type of IBS patients recruited, with 1 study recruiting IBS-M patients (259), and the other IBS-D patients (260).

Both trials provided total numbers of adverse events. There were no adverse events in either arm in one RCT (259) and four adverse events in each arm of the other trial (260).

10. Serotonergic agents

We suggest alosetron for overall symptom improvement in female IBS-D patients

Recommendation: Weak

Quality of evidence: Low

Serotonin (5-hydroxytryptamine; 5-HT) is implicated in GI secretion, motility, and sensation (261), and a variety of 5-HT receptors have been targets for new drug development in FGIDs (262). Alosetron, a selective 5-HT_3 antagonist was evaluated in IBS-D and, although it showed efficacy, reports of severe constipation and ischemic colitis led to its withdrawal by the FDA in 2001 (263). It was re-introduced, via a risk evaluation and mitigation strategy (REMS) for "women suffering with severe IBS-D that is disabling". The initial dose of 0.5mg b.i.d. used via this REMS is lower than that used in the pivotal trials. Other 5-HT_3 antagonists, such as cilansetron and ramosetron, have never been introduced into clinical practice in the US.

Tegaserod is a partial, selective 5-HT_4 agonist, which was granted FDA approval for use in women with IBS-C in 2002. It was withdrawn in 2007, due to possible cardiovascular adverse effects. Tegaserod is the only 5-HT_4 partial agonist that has been evaluated in large, prospective, RCTs in IBS patients. As the drug is no longer available in the US, an updated analysis has not been performed. The interested reader is referred to the previous systematic review (264).

We identified no new studies of alosetron since the previous version of the monograph (4). There were therefore eight RCTs (265-272), recruiting 4987 patients. Only one trial was at low risk of bias (272), with the remainder unclear. Most trials

recruited women only, or predominantly women, with the exception of a US-based trial that recruited only men (271).

Overall, there was a statistically significant effect in favor of alosetron (RR = 0.79; 95% CI 0.69 to 0.90), with a NNT of 7.5 (95% CI 5 to 16), but significant heterogeneity between studies (I^2 = 85%, P < 0.001) (Table 1). The quality of evidence was rated as low because of concerns around risk of bias and unexplained heterogeneity between studies. There were seven studies evaluating 4607 patients that provided total adverse events data (266-272). There were significantly more adverse events with alosetron than placebo (RR = 1.19; 95% CI 1.09 to 1.30). The NNH was 10 (95% CI 6 to 20). The main adverse event that was more common with alosetron than with placebo was constipation (NNH = 5; 95% CI 3 to 8).

11. Polyethylene Glycol (PEG)

We suggest against PEG for overall symptom improvement in IBS patients

Recommendation: Weak

Quality of evidence: Low

PEG is an osmotic laxative that is not absorbed in the intestinal lumen and is widely available. Its efficacy for constipation has been well established in RCTs (273). However, its clinical effects in patients with IBS-C are less certain.

Since the previous monograph (4), no new trials were identified, meaning that there were two RCTs assessing PEG in IBS patients. In one RCT at unclear risk of bias (274), containing 42 patients, although bowel movement frequency increased from baseline for both PEG and placebo arms, no statistically significant effect on

bowel movements, or pain or discomfort was reported between the active and placebo arms. In the second study (275), which was also at unclear risk of bias and recruited 139 patients with IBS-C, there was an increase in spontaneous bowel movements compared with placebo at 4 weeks. Although pain scores decreased from baseline, no significant effect on abdominal pain or discomfort was seen with PEG compared with placebo. There was also a trend toward greater improvement in bloating in the PEG arm (P = 0.06). Adverse event rates were slightly higher in patients receiving PEG compared with placebo in one RCT (38.8% vs. 32.9%; 16.4% vs. 8.6% of which were possibly/probably treatment-related) (275). The most common treatment-related symptoms were abdominal pain (6% vs. 0%), and diarrhea (4.5% vs. 4.3%).

Summary:

PEG improved frequency of bowel movements in IBS-C, but not pain or other IBS-related symptoms.

12. 5-aminosalicylates in IBS

We suggest against 5-aminosalicylates (5-ASAs) for overall symptom improvement in IBS patients

Recommendation: Weak

Quality of evidence: Low

Based on studies in post-infectious IBS (276), as well as IBS in general (277, 278), that a state of low grade-inflammation or immune activation is present in some subjects, the hypothesis that anti-inflammatory compounds, such as those used widely

in inflammatory bowel disease (279, 280), might be effective in IBS has been explored.

We identified three RCTs of 5-ASAs in IBS (281-283), all of which used mesalamine, and contained 464 patients. Two RCTs were at low risk of bias (281, 282). One trial used a dose of either 750 mg or 1.5g mesalamine o.d. (283), one trial used a dose of 2g b.i.d. (282), and the third used 800mg t.i.d. (281). All individual studies were negative, according to their primary end-points, evaluating all doses of 5-ASA. When all data were pooled according to predefined criteria for this monograph there was a significant effect of mesalamine in reducing symptoms in IBS compared with placebo (RR of IBS symptoms not improving = 0.85; 95% CI 0.75 to 0.97), and no significant heterogeneity between individual trial results (I^2 =0%, P = 0.45) (Table 1). The NNT with mesalamine was 9 (95% CI 5 to 50). However, this result was not robust and, if author-defined primary end-points were used, the results were not statistically significant (RR = 0.90; 95% CI = 0.77 to 1.06). Data on overall adverse events were not reported in any of the three trials. Individual adverse events were reported in two trials (281, 282), but were rare, and none were more frequent with mesalamine.

Summary:

Although our systematic review did suggest a benefit of 5-ASAs in relieving IBS symptoms, this result depended on the end-point used, and the Task Force felt that the data were too fragile to recommend this intervention in IBS. These data, however, suggest that 5-ASAs should be further studied in adequately powered RCTs in IBS, as there is a possibility that these drugs may be modestly efficacious in improving symptoms.

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Table 1.Summary of Evidence from Randomized Controlled Trials of Pharmacological, Psychological, and Dietary Therapies in Irritable Bowel Syndrome.

Intervention	Number of RCTs	Number of patients	IBS subtype	Relative risk of remaining symptomatic vs. placebo (95% CI)	Heterogeneity (I^2 value)	Number needed to treat (95% CI)	Recommendation and Strength of Evidence
Exercise	2	158	Not stated	No dichotomous data reported	No dichotomous data reported	No dichotomous data reported	Weak, very low
Low FODMAP diet	7	397	Not stated	0.69 (0.54 to 0.88)	52%	5 (3 to 11)	Weak, very low
Gluten-free diet	2	111	Not stated	0.46 (0.16 to 1.28)	86%	N/A	Weak, very low
Fiber **Insoluble fiber e.g. bran** **Soluble fiber e.g. psyllium**	15 6 7	946 441 499	Not stated Not stated Not stated	0.87 (0.80 to 0.94) 0.90 (0.79 to 1.03) 0.83 (0.73 to 0.94)	0% 0% 18%	11 (7 to 25) N/A 7 (4 to 25)	Strong, moderate
Prebiotics	1	128	IBS-D	No dichotomous data reported	No dichotomous data reported	No dichotomous data reported	Weak, very low

Synbiotics	2	198	Not stated	Only one RCT reported dichotomous data	Only one RCT reported dichotomous data	Only one RCT reported dichotomous data	Weak, very low
Probiotics	37	4403	Not stated	0.81 (0.74 to 0.88)	71%	7 (5 to 12)	Weak, low
Antibiotics (rifaximin)	6	2441	IBS-D or IBS-M	0.86 (0.81 to 0.91)	0%	10.5 (8 to 16)	Weak, moderate
Antispasmodics	26	2811	Not stated	0.65 (0.56 to 0.76)	69%	5 (4 to 8)	Weak, very low
Peppermint oil	7	634	Not stated	0.54 (0.39 to 0.76)	73%	4 (3 to 6)	Weak, low
Antidepressants **Tricyclic antidepressants** **Selective serotonin re-uptake inhibitors**	18 12 7	1127 787 356	Not stated Not stated Not stated	0.66 (0.57 to 0.76) 0.65 (0.55 to 0.77) 0.68 (0.51 to 0.91)	37% 34% 49%	4 (3.5 to 6) 4 (3.5 to 7) 5 (3 to 16.5)	Strong, high Weak, low
Psychological therapies	36	2487	Not stated	0.69 (0.62 to 0.76)	69%	4 (3.5 to 5.5)	Weak, very low
Linaclotide	4	2867	IBS-C	0.81 (0.77 to 0.85)	0%	6 (5 to 8)	Strong, high
Plecanatide	3	2612	IBS-C	0.88 (0.84 to 0.92)	0%	10 (8 to 14)	Strong, moderate
Lubiprostone	3	1366	IBS-C	0.91 (0.87 to 0.95)	0%	12.5 (8 to 25)	Strong, moderate
Eluxadoline	3	3235	IBS-D	0.91 (0.85 to 0.97)	66%	12.5 (8 to 33)	Weak, moderate
Loperamide	2	42	IBS-D or IBS-M	0.44 (0.14 to 1.42)	54%	N/A	Strong, very low

Alosetron	8	4987	IBS-D	0.79 (0.69 to 0.90)	85%	7.5 (5 to 16)	Weak, low
Polyethylene glycol	2	181	IBS-C	No dichotomous data reported	No dichotomous data reported	No dichotomous data reported	Weak, low
5-aminosalicylates (mesalamine)	3	464	IBS-D in two RCTs	0.85 (0.75 to 0.97)	0%	9 (5 to 50)	Weak, low