CME

American College of Gastroenterology Monograph on the Management of Irritable Bowel Syndrome and Chronic Idiopathic Constipation

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Irritable bowel syndrome (IBS) and chronic idiopathic constipation ((CIC) also referred to as functional constipation) are two of the most common functional gastrointestinal disorders worldwide. IBS is a global problem, with anywhere from 5 to 15% of the general population experiencing symptoms that would satisfy a definition of IBS (1,2). In a systematic review on the global prevalence of IBS, Lovell and Ford (1) documented a pooled prevalence of 11% with all regions of the world suffering from this disorder at similar rates. Given its prevalence, the frequency of symptoms, and their associated debility for many patients and the fact that IBS typically occurs in younger adulthood, an important period for furthering education, embarking on careers, and/or raising families, the socioeconomic impact of IBS is considerable. These indirect medical costs are frequently compounded by the direct medical costs related to additional medical tests and the use of various medical and nonmedical remedies that may have limited impact. CIC is equally common; in another systematic review, Suares and Ford (3) reported a pooled prevalence of 14%, and also noted that constipation was more common in females, in older subjects, and those of lower socioeconomic status (3). Chronic constipation has also been linked to impaired quality of life (4), most notably among the elderly (5).

Neither IBS nor CIC are associated with abnormal radiologic or endoscopic abnormalities, nor are they associated with a reliable biomarker; diagnosis currently rests entirely, therefore, on clinical grounds. Although a number of clinical definitions of both IBS and CIC have been proposed, the criteria developed through the Rome process, currently in its third iteration, have been those most widely employed in clinical trials and, therefore, most relevant to any review of the literature on the management of these disorders.

According to Rome III, IBS is defined on the basis of *the presence of:*

Recurrent abdominal pain or discomfort at least 3 days/month in the past 3 months associated with two or more of the following:

- Improvement with defecation
- Onset associated with a change in frequency of stool
- Onset associated with a change in form (appearance) of stool

These criteria should be fulfilled for the past 3 months with symptom onset at least 6 months before diagnosis (6).

Rome III defines functional constipation as: the presence of two or more of the following:

- Straining during at least 25% of defecations
- Lumpy or hard stools in at least 25% of defecations
- Sensation of incomplete evacuation for at least 25% of defecations
- Sensation of anorectal obstruction/blockage for at least 25% of defecations
- Manual maneuvers to facilitate at least 25% of defecations (e.g., digital evacuation, support of the pelvic floor)
- Fewer than three defecations per week

Furthermore, loose stools are rarely present without the use of laxatives and there are insufficient criteria for IBS. Again, these criteria should be fulfilled for the past 3 months with symptom onset at least 6 months before diagnosis (6).

In Rome III, IBS is subtyped according to predominant bowel habit as IBS with constipation (IBS-C), IBS with diarrhea (IBS-D), mixed type (IBS-M), and unclassified (IBS-U). The definition of

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bowel habit type is, in turn, based on the patient's description of stool form by referring to the Bristol Stool Scale (7). The recognition that IBS sufferers segregate into subtypes according to predominant bowel habit, together with research findings suggesting that IBS-C and IBS-D may be pathophysiologically distinct entities (8–10), led to the development of therapies specifically directed at each of these subtypes. Nonetheless, it is worth noting that symptoms may not be stable over a lifetime and individuals may exhibit one IBS subtype during a period, and then a different IBS subtype during another period in their lives.

However, although there is general awareness of the Rome criteria, they are infrequently employed in the assessment of IBS and CIC in clinical practice (11). To provide more "clinician friendly" definitions, as well as to permit inclusion of studies that predated the Rome process, American College of Gastroenterology Task Forces suggested the following definitions in prior systematic reviews:

IBS is defined by: *abdominal discomfort associated with altered bowel habits* (12).

Constipation is defined as: *a symptom-based disorder defined as unsatisfactory defecation and is characterized by infrequent stools, difficult stool passage, or both.* Difficult stool passage includes straining, a sense of difficulty passing stool, incomplete evacuation, hard/lumpy stools, prolonged time to stool, or need for manual maneuvers to pass stool. CIC is defined as the presence of these symptoms for at least 3 months (13).

It is important to note that the Rome III criteria state that i ndividuals with chronic constipation do not fulfill criteria for IBS, with pain or discomfort being a major determinant in the latter. In practice, a clear separation between CIC and IBS with constipation may be challenging and studies have shown, not only considerable overlap between these entities (14–16), but also a significant tendency for patients to migrate between these diagnoses over time (15). It is appropriate therefore that in this update of prior American College of Gastroenterology monographs on IBS and CIC, these entities be addressed in the same exercise (12,13,17). The goal of this exercise, therefore, was to update the most recent systematic reviews commissioned by the American College of Gastroenterology on IBS from 2009 (17) and CIC from 2005 (13).

METHODS

We have conducted a series of systematic reviews on the efficacy of therapy in IBS and CIC. There have been several systematic reviews of therapy for IBS and CIC published in the past 5 years (18–22). There have been considerable data published in the intervening time, and hence we have, therefore, updated all these systematic reviews of IBS and CIC and synthesized the data, including the information from new trials, where appropriate.

The primary objective of this exercise was to assess the efficacy of available therapies in treating IBS and CIC compared with placebo or no treatment. The secondary objectives included assessing the efficacy of available therapies in treating IBS according to predominant stool pattern reported (IBS with constipation, IBS with diarrhea, and mixed IBS), as well as assessing adverse events with therapies for both IBS and CIC.

Systematic review methodology

We evaluated manuscripts that studied adults (aged >16 years) using any definition of IBS or CIC. For IBS, this included a clinician-defined diagnosis, the Manning criteria (23), the Kruis score (24), or Rome I (25), II (26), or III (6) criteria. For CIC, this included symptoms diagnosed by any of the Rome criteria (6,25,26), as well as a clinician-defined diagnosis. We included only parallel-group randomized controlled trials (RCTs) comparing active intervention with either placebo or no therapy. Crossover trials were eligible for inclusion, provided extractable data were provided at the end of the first treatment period, before crossover.

For IBS, the following treatments were considered:

1. Diet and dietary manipulation
2. Fiber
3. Interventions that modify the microbiota: probiotics, prebiotics, antibiotics
4. Antispasmodics
5. Peppermint oil
6. Loperamide
7. Antidepressants
8. Psychological therapies, including hypnotherapy
9. Serotonergic agents
10. Prosecretory agents
11. Polyethylene glycol

For CIC, the following were considered:

1. Fiber
2. Osmotic and stimulant laxatives
3. 5-HT_4 agonists
4. Prosecretory agents
5. Biofeedback
6. Bile acid transporter inhibitors
7. Probiotics

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

(i) Global assessment of improvement in IBS or CIC symptoms
(ii) Improvement in abdominal pain for IBS
(iii) Global IBS symptom or abdominal pain scores for IBS
(iv) Mean number of stools per week during therapy for CIC

Search strategy for identification of studies

MEDLINE (1946 to October 2013), EMBASE and EMBASE Classic (1947 to October 2013), and the Cochrane central register of controlled trials were searched.

Studies on IBS were identified with the terms *irritable bowel syndrome* and *functional diseases*, *colon* (both as medical subject

headings (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*, *fructose*, *lactose intolerance*, or *lactose* (both as MeSH and free text terms), or the following free text terms: *FODMAP$*, *glutens*, *food adj5 intolerance*, *food allergy*, or *food hypersensitivity*.

For RCTs of fiber, antispasmodics, and peppermint oil, these were combined using the set operator AND with studies identified with the terms: *dietary fiber*, *cereals*, *psyllium*, *methylcellulose*, *sterculia*, *karaya gum*, *parasympatholytics*, *hyoscyamine*, *scopolamine*, *trimebutine*, *muscarinic antagonists*, or *butylscopolammonium bromide* (both as MeSH and free text terms), or the following free text terms: *bulking agent*, *psyllium fiber*, *fiber*, *husk*, *bran*, *ispaghula*, *wheat bran*, *calcium polycarbophil*, *spasmolytics*, *spasmolytic agents*, *antispasmodics*, *mebeverine*, *alverine*, *pinaverium bromide*, *otilonium bromide*, *cimetropium bromide*, *hyoscine butyl bromide*, *butylscopolamine*, *peppermint oil*, or *colpermin*.

For RCTs of probiotics, these were combined using the set operator AND with studies identified with the terms: *Saccharomyces*, *Lactobacillus*, *Bifidobacterium*, *Escherichia coli*, or *probiotics* (both as MeSH and free text terms). For RCTs of prebiotics and synbiotics, these were combined using the set operator AND with studies identified with the term: *prebiotic* (both MeSH and free text terms) or *synbiotic* (both MeSH and free text terms). For RCTs of antibiotics, these were combined using the set operator AND with studies identified with the terms: *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 *rifamixin*.

For RCTs of 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), or the following free text terms: *imodium* or *lopex*.

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 reuptake inhibitors*, *paroxetine*, *sertraline, fluoxetine*, *citalopram*, *venlafaxine*, *cognitive therapy*, *psychotherapy*, *behavior therapy*, *relaxation techniques*, or *hypnosis* (both as MeSH and free text terms), or the following free text terms: *behavioral therapy*, *relaxation therapy*, or *hypnotherapy*.

For RCTs of serotonergic agents, these were combined using the set operator AND with studies identified with the terms: *serotonin antagonists*, *serotonin agonists*, *cisapride*, *receptors* (*serotonin*, *5-HT$_3$*), or *receptors* (*serotonin*, *5-HT$_4$*) (both as MeSH and free text terms), or the following free text terms: *5-HT$_3$*, *5-HT$_4$*, *alosetron*, *cilansetron*, *ramosetron*, *prucalopride*, *mosapride*, or *renzapride*.

For RCTs of pro-secretory agents, these were combined using the set operator AND with studies identified with the following free text terms: *linaclotide* or *lubiprostone*.

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

Studies on CIC were identified with the terms *constipation* or *gastrointestinal transit* (both as MeSH and free text terms), or *functional constipation*, *idiopathic constipation*, *chronic constipation*, or *slow transit* (as free text terms). For the search involving biofeedback, the free text terms *dyssynergia*, *pelvic floor dysfunction*, *anismus*, and *outlet obstruction* were also added.

For RCTs of fiber, these were combined using the set operator AND with studies identified with the terms: *dietary fiber*, *cellulose*, *plant extracts*, *psyllium*, *cereals*, *plantago*, or *methylcellulose* (both as MeSH and free text terms), or the following free text terms: *fiber*, *soluble fiber*, *insoluble fiber*, *bran*, *ispaghula*, *metamucil*, *fybogel*, or *ispaghula*.

For RCTs of osmotic and stimulant laxatives, these were combined using the set operator AND with studies identified with the terms: *laxatives*, *cathartics*, *anthraquinones*, *phenolphthaleins*, *indoles*, *phenols*, *lactulose*, *polyethylene glycol*, *senna plant*, *senna extract*, *bisacodyl*, *phosphates*, *dioctyl sulfosuccinic acid*, *magnesium*, *magnesium hydroxide*, *sorbitol*, *poloxamer* (both as MeSH and free text terms), or the following free text terms: *sodium picosulphate*, *docusate*, *milk of magnesia*, *danthron*, *senna*, and *poloxalkol*.

For RCTs of 5-HT$_4$ agonists, these were combined using the set operator AND with studies identified with the terms: *serotonin agonists, receptors*, or *serotonin*, *5-HT$_4$* (both as MeSH and free text terms), or the following free text terms: *prucalopride*, *velusetrag*, or *naronapride*.

For RCTs of pro-secretory agents, these were combined using the set operator AND with studies identified with the following free text terms: *lubiprostone* or *linaclotide*.

For RCTs of biofeedback, these were combined using the set operator AND with studies identified with the MESH terms *biofeedback* and *psychology* and the following free text terms: *biofeedback* or *neuromuscular training*.

For RCTs of bile acid transporter inhibitors, these were combined using the set operator AND with studies identified with the following free text terms: *bile acid transporter*, *elobixibat*, or *A3309*.

For RCTs of probiotics, these were combined using the set operator AND with studies identified with the terms: *Saccharomyces*, *Lactobacillus*, *Bifidobacterium*, *E. coli*, or *probiotics* (both as MeSH and free text terms). For RCTs of prebiotics and synbiotics, these were combined using the set operator AND with studies identified with the term: *prebiotic* (both MESH and free text terms) or *synbiotic* (both MESH and free text terms).

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. DDW (Digestive Diseases Week) and UEGW (United European

Gastroenterology Week) abstract books were hand searched between 2000 and 2013. Authors of trial reports that did not give enough detail for adequate data extraction were contacted and asked to contribute full data sets. Experts in the field were contacted for leads on unpublished studies.

Trials were assessed for risk of bias according to the methods described in the Cochrane handbook [27] using the following characteristics: method used to generate the randomization schedule, method used to conceal treatment allocation, implementation of masking, completeness of follow-up, and conduct of an intention-to-treat analysis.

Eligibility, quality, and outcome data were extracted by the lead reviewer (Alexander Ford) and by a masked second reviewer (Paul Moayyedi) on to specially developed forms. Any discrepancy was resolved by discussion between the two reviewers in order to reach a consensus. Data were extracted as intention-to-treat analyses, where all dropouts were assumed to be treatment failures, wherever trial reporting allowed this.

Data synthesis

For IBS, whenever possible, *any improvement of global IBS symptoms* as a binary outcome was taken as the primary outcome measure. If this was not available, *improvement in abdominal pain* was used. For CIC, *any improvement of global CIC symptoms* as a binary outcome was taken as the primary outcome measure. The impact of interventions was expressed as a relative risk (RR) of IBS or CIC symptoms not improving, together with 95% confidence intervals (CIs). If there were sufficient data, RRs were combined using the DerSimonian and Laird random effects model (28) to give a more conservative estimate of the efficacy of individual IBS therapies. For continuous data, such as global IBS symptom scores or individual IBS symptom scores, a standardized mean difference, with 95% CIs, was calculated. It should be noted that some treatments may be beneficial in IBS or CIC because of the effects on outcomes other than global symptoms or abdominal pain, but this was not evaluated and was outside of the scope of this review.

Tests of heterogeneity were reported (29). When the test of heterogeneity was significant ($P<0.10$ and/or $I^2>25\%$), the reasons for this were explored by evaluating differences in study population, study design, or study end points in subgroup analyses. Publication bias or other causes of small study effects were evaluated using tests for funnel plot asymmetry (30), where sufficient studies were identified (31).

The number needed to treat (NNT), which is the number of patients who would need to receive active therapy, over and above the control therapy, for one to experience an improvement in symptoms, and the number needed to harm (NNH), which is the number of patients who would need to receive active therapy, over and above the control therapy, for one to experience an adverse event were calculated as the inverse of the risk difference from the meta-analysis and checked using the formula: $\mathrm{NNT} = 100 / \mathrm{RRR} \times \mathrm{BR}$, where BR is baseline risk and RRR is relative risk reduction.

Box 1. Interpretation of the grading of the quality of evidence

Quality of evidence	Interpretation
High	Further research is very unlikely to change our confidence in the estimate of effect.
Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low	The estimate of effect is very uncertain.

From: http://www.gradeworkinggroup.org.

Methodology for assessing levels of evidence and grading recommendations

We used the GRADE (Grading of Recommendations Assessment, Development and Evaluation) system for grading the quality of evidence and strength of recommendation for each medical intervention (32). The system has been widely used in evidence-based guidelines and is endorsed by all major gastrointestinal societies (http://www.gradeworkinggroup.org). The quality of the evidence is based on the study design, as well as the extent of risk of bias, inconsistency, indirectness, imprecision, and publication bias that exists for the evidence supporting the intervention (33). Quality of evidence is described as high to very low, depending on the extent to which further evidence would change the estimate of treatment effect (**Box 1**). The grading scheme also classifies recommendations as strong or weak, according to the quality of the evidence, applicability to all patient groups, balance of benefits and risks, patient preferences, and cost. With this graded recommendation, the clinician receives guidance about whether or not recommendations should be applied to most patients, and whether or not recommendations are likely to change in the future after production of new evidence. "Strong" recommendations represent a "recommendation that can apply to most patients in most circumstances and *further evidence is unlikely to change our confidence in the estimate of treatment effect.*" The summary of the evidence for IBS is presented in **Table 1**, the reasons for the decision on the quality of that evidence in **Table 2**, and the reasons for the strength of recommendation in **Table 3**. Similarly, the summary of the evidence for CIC is presented in **Table 4**, the reasons for the decision on quality of the evidence in **Table 5**, and the reasons for the strength of recommendation in **Table 6**.

RESULTS

Irritable bowel syndrome

1. Diet and dietary manipulation in IBS

(a) Role of diet in IBS: Although food intake is one of the most common precipitants of symptoms in IBS (34), responses to food ingestion and interactions with components of the diet have not typically undergone rigorous evaluation in the context of a blinded trial. Based on their own experiences, IBS sufferers have generated their own theories to explain this phenomenon or seek guidance from other, usually unsupported, dietary remedies.

Table 1. Summary of results of monograph on interventions for IBS

Statement	No. of trials	No. of patients	RR symptoms (95% CI)	NNT (95% CI)	Recommendation	Quality of evidence
Specialized diets may improve symptoms in individual IBS patients.	3	230	NA	NA	Weak	Very low
Fiber provides overall symptom relief in IBS.	14	906	0.86 (0.80–0.94)	10 (6–33)	Weak	Moderate
Psyllium, but not bran, provides overall symptom relief in IBS (data presented for psyllium).	7	499	0.83 (0.73–0.94)	7 (4–25)	Weak	Moderate
There is insufficient evidence to recommend prebiotics or synbiotics in IBS.	2	198	NA	NA	Weak	Very low
Taken as a whole, probiotics improve global symptoms, bloating, and flatulence in IBS.	23	2,575	0.79 (0.70–0.89)	7 (4–12.5)	Weak	Low
Rifaximin is effective in reducing total IBS symptoms and bloating in IBS-D.	5	1,805	0.84 (0.78–0.90)	9 (6–12.5)	Weak	Moderate
Certain antispasmodics provide symptomatic short-term relief in IBS.	23	2,154	0.69 (0.59–0.81)	5 (4–9)	Weak	Low
Peppermint oil is superior to placebo in improving IBS symptoms.	5	482	0.51 (0.33–0.79)	3 (2–4)	Weak	Moderate
There is insufficient evidence to recommend loperamide for use in IBS.	2	42	0.44 (0.14–1.42)	NA	Strong	Very low
As a class, antidepressants are effective in symptom relief in IBS.	17	1,084	0.67 (0.58–0.77)	4 (3–6)	Weak	High
A variety of psychological interventions are effective in improving IBS symptoms.	32	2,189	0.68 (0.61–0.76)	4 (3–5)	Weak	Very low
Alosteron is effective in females with IBS-D.	8	4,987	0.79 (0.69–0.90)	8 (5–17)	Weak	Moderate
Mixed 5-HT_4 agonists/5-HT_3 antagonists are not more effective than placebo at improving symptoms of IBS-C.	9	2,905	0.96 (0.83–1.11)	NA	Strong	Low
Linaclotide is superior to placebo for the treatment of IBS-C.	3	2,028	0.80 (0.75–0.85)	6 (5–8)	Strong	High
Lubiprostone is superior to placebo for the treatment of IBS-C.	3	1,366	0.91 (0.87–0.95)	12.5 (8–25)	Strong	Moderate
There is no evidence that polyethylene glycol improves overall symptoms and pain in patients with IBS.	2	166	NA	NA	Weak	Very low

CI, confidence interval; 5-HT_3, serotonin subtype 3; 5-HT_4, serotonin subtype 4; IBS, irritable bowel syndrome; IBS-C, IBS with constipation; IBS-D, IBS with diarrhea; NA, not available; NNT, number needed to treat; RR, relative risk.

Many IBS patients commonly believe that they have an allergy to certain foods, although true food allergies are uncommon in IBS (35). Thus, although the prevalence of true food allergies in Western societies is between 1 and 3% in adults, surveys of gastrointestinal clinic patients found that 30–50% believed that their symptoms represented food allergy or food intolerance (35–37). Most food-related IBS symptoms appear to represent food intolerance, although only 11–27% of patients can accurately identify the presumed offending food when re-challenged in a double-blind manner (38). Based on their own experiences with food, and despite a lack of objective evidence to incriminate a specific food, studies have shown that a majority of IBS patients institute dietary changes (39–41), sometimes to an extent that may compromise their nutrition (42).

(b) Role of dietary manipulation in IBS: Specialized diets may improve symptoms in individual IBS patients.
Recommendation: weak. Quality of evidence: very low.

We identified 12 RCTs that evaluated dietary intervention in IBS (43–54). Following exclusions due to nonextractable data (46,48,50,52–54), lack of relevant symptom data (45,49,51), and an intervention lasting <1 week (46), three evaluable RCTs involving 230 patients remained (43,44,47).

The first of these addressed the impact of gluten in IBS. In a double-blind, placebo-controlled trial, 34 patients with IBS were randomized to either remain on a gluten-free diet or to receive 16 g/day of gluten on completion of an open gluten-free run-in phase (44). In the gluten group, 68% (13/19) reported that their

Table 2. Reasons for quality of evidence of assessment for IBS data according to GRADE criteria

Statement	Quality assessment	Study limitations	Inconsistency	Indirectness of evidence	Imprecision	Reporting bias
Specialized diets may improve symptoms in individual IBS patients.	Very low	Only one low risk of bias trial	Each eligible RCT evaluated a different intervention	✓[a]	Only a small number of patients studied	Not evaluable
Fiber provides overall symptom relief in IBS.	Moderate	Only one low risk of bias trial and two high risk of bias	✓	✓	✓	✓
Psyllium, but not bran, provides overall symptom relief in IBS.	Moderate	Only one low risk of bias trial but this contributed to almost half the total number of patients and this trial mirrored the result of the meta-analysis	✓	Only one trial compared the two types of fibers. This trial confirmed the result of the systematic review at week 4 but not at week 12	✓	✓
There is insufficient evidence to recommend prebiotics or synbiotics in IBS.	Very low	Only one synbiotic trial with dichotomous data. Overall result positive. Meta-analysis of continuous data from two trials showed no benefit	Differences in efficacy between the dichotomous and continuous data. Each trial evaluated a different preparation	✓	Only a small number of patients studied	Not evaluable
Taken as a whole, probiotics improve global symptoms, bloating, and flatulence in IBS.	Low	✓	Significant heterogeneity between studies that was unexplained. Inconsistency considered very serious as most studies evaluated different probiotics	✓	✓	✓
Rifaximin is effective in reducing total IBS symptoms and bloating in IBS-D.	Moderate	✓	✓	✓	The impact of antibiotics on IBS symptoms was modest	✓
Certain antispasmodics provide symptomatic short-term relief in IBS.	Low	All trials unclear risk of bias and the effect on IBS symptoms was marked.	Significant heterogeneity between studies that was unexplained. Only a small number of studies evaluating each type of drug	✓	✓	There was funnel plot asymmetry suggesting reporting bias or other small study effects
Peppermint oil is superior to placebo in improving IBS symptoms.	Moderate	Only one low risk of bias trial and this study was the least positive (although still showing statistically significant benefit compared to placebo). Quality of evidence upgraded as effect on IBS symptoms marked	Significant heterogeneity between studies that was unexplained	✓	✓	Not evaluable
There is insufficient evidence to recommend loperamide for use in IBS.	Very low	Both trials have unclear risk of bias	Significant heterogeneity between studies that was unexplained	✓	Effect not significant and confidence intervals very wide	Not evaluable
As a class, antidepressants are effective in symptom relief in IBS.	High	Three low risk of bias trials. Meta-analysis of these showed statistically significant effect of antidepressants vs. placebo	✓	✓	✓	✓
A variety of psychological interventions are effective in improving IBS symptoms.	Very low	All trials high risk of bias	Significant heterogeneity between studies that was unexplained	Most RCTs did not have an adequate control group	✓	There was funnel plot asymmetry suggesting reporting bias or other small study effects
Alosteron is effective in females with IBS-D.	Moderate	Only one trial had low risk of bias but this trial was also positive and large	Significant heterogeneity between studies that was unexplained	✓	✓	✓

Table 2 continued on following page

Table 2. Continued

Statement	Quality assessment	Study limitations	Inconsistency	Indirectness of evidence	Imprecision	Reporting bias
Mixed 5-HT_4 agonists/5-HT_3 antagonists are not more effective than placebo at improving symptoms of IBS-C.	Low	Only one trial was low risk of bias and this study was negative	Significant heterogeneity between studies that was unexplained	✓	✓	✓
Linaclotide is superior to placebo for the treatment of IBS-C.	High	✓	✓	✓	✓	Not evaluable
Lubiprostone is superior to placebo for the treatment of IBS-C.	Moderate	One other RCT performed but unable to obtain dichotomous data from the company or authors	✓	✓	Effect modest	✓
There is no evidence that polyethylene glycol improves overall symptoms and pain in patients with IBS.	Very low	Both trials are unclear risk of bias	RCTs cannot be combined as different populations studied	✓	No statistically significant effect on abdominal pain or overall symptoms. Overall number of patients studied was small	Not evaluable

GRADE, Grading of Recommendations Assessment, Development and Evaluation; 5-HT_3, serotonin subtype 3; 5-HT_4, serotonin subtype 4; IBS, irritable bowel syndrome; IBS-C, IBS with constipation; IBS-D, IBS with diarrhea; RCT, randomized controlled trial.
[a]Check marks indicate that the criterion was fulfilled/not a concern.

symptoms were not adequately controlled as compared with 6/15 (40%) in the placebo group. Continuous symptom scores for abdominal pain, bloating, satisfaction with stool consistency, and tiredness were statistically significantly better in those who maintained a gluten-free diet.

The second of these studies examined the contribution of food allergy or hypersensitivity as assessed, not by immunoglobulin (Ig) E antibodies, but by IgG antibodies (43). In a double-blind, parallel-group trial, 150 IBS patients were randomized to either an exclusion diet based on the presence of IgG antibodies to various foods or a sham diet. Participants were followed for 12 weeks and symptoms assessed using a global impact score and the IBS severity score. Compared with 11/66 (17%) in the sham diet group ($P=0.14$), 28% (18/65) in the exclusion diet intervention arm noted a significant improvement in symptoms. The authors reported marginal statistical significance in those with high adherence to their diet.

The third study examined the role of FODMAPs (fermentable oligosaccharides, disaccharides, monosaccharides, and polyols). Forty-one IBS patients were randomized to a low-FODMAP diet or their regular (habitual) diet for 4 weeks (47). Of those randomized to the low-FODMAP diet, 68% (13/19) reported adequate control of their symptoms compared with 5/22 (23%) of the habitual diet group ($P=0.005$). Stool consistency did not differ between groups; stool frequency was less in the low-FODMAP diet group. A significant limitation of this study was the lack of blinding regarding the dietary intervention.

Summary: Belatedly perhaps, the role of dietary components in the precipitation of symptoms, or even in the basic pathogenesis of IBS, is now being addressed. To date, two mechanisms, intolerance and hypersensitivity, have been addressed in clinical trials, although it is highly plausible that other mechanisms (e.g., stimulation of gut hormones and interactions with the microbiota) may also be relevant to the effects of food or food components. While recognizing the challenges that any investigation of the role of an individual's diet or of a specific food component in IBS present, the current data provide limited guidance on the role of diet in the management of IBS. Gluten-free and low-FODMAP diets show promise but their precise role(s) in the management of IBS need to be defined.

2. Fiber in IBS

Fiber provides overall symptom relief in IBS.
Recommendation: weak. Quality of evidence: moderate.
Psyllium, but not bran, provides overall symptom relief in IBS.
Recommendation: weak. Quality of evidence: moderate.

Increased intake of dietary fiber is frequently recommended to improve bowel function for IBS, particularly for constipation-related symptoms. However, insoluble fibers frequently cause bloating and abdominal discomfort.

In updating our prior systematic review (18), we identified two additional studies for a total of 14 RCTs (55–69) involving 906 patients. All but five trials did not differentiate IBS by subtype and only two restricted recruitment to IBS-C (58,66).

Table 3. Reasons for strength of recommendation for IBS therapies according to GRADE criteria

Statement	Recommendation	Quality of evidence	All patient groups	Benefits vs. risks	Patient values	Cost[a]
Specialized diets may improve symptoms in individual IBS patients.	Weak	Very low	Likely to relate to only some IBS patients	Some diets are very stringent and difficult to follow	✓[b]	✓
Fiber provides overall symptom relief in IBS.	Weak	Moderate	May only relate to IBS-C, most trials did not state type of IBS patient	Fiber can cause bloating and abdominal discomfort	Some patients do not like taking fiber supplements	✓
Psyllium, but not bran, provides overall symptom relief in IBS.	Weak	Moderate	May only relate to IBS-C, most trials did not state type of IBS patient	Fiber can cause bloating and abdominal discomfort	Some patients do not like taking fiber supplements	✓
There is insufficient evidence to recommend prebiotics or synbiotics in IBS.	Weak	Very low	Likely that only some patients will respond	✓	✓	Can be expensive to patients
Taken as a whole, probiotics improve global symptoms, bloating, and flatulence in IBS.	Weak	Low	Likely that only some patients will respond	✓	✓	Can be expensive to patients
Rifaximin is effective in reducing total IBS symptoms and bloating in IBS-D.	Weak	Moderate	Likely that only some patients will respond	Antibiotic resistance of GI flora a concern if use widespread. Long-term efficacy uncertain	✓	Can be expensive to patients
Certain antispasmodics provide symptomatic short-term relief in IBS.	Weak	Low	✓	✓	✓	✓
Peppermint oil is superior to placebo in improving IBS symptoms.	Weak	Moderate	✓	✓	✓	✓
There is insufficient evidence to recommend loperamide for use in IBS.	Strong	Very low	✓	✓	✓	✓
As a class, antidepressants are effective in symptom relief in IBS.	Weak	High	✓	Both TCA and SSRI associated with adverse events with an NNH of 9.	Some patients do not like the idea of taking antidepressants	SSRIs can be expensive. TCAs are inexpensive.
A variety of psychological interventions are effective in improving IBS symptoms.	Weak	Very low	✓	Can be time intensive for patients	Some patients do not like the concept of psychotherapy	Most psychotherapeutic interventions are expensive
Alosteron is effective in females with IBS-D.	Weak	Moderate	✓	Concerns regarding ischemic colitis	✓	Can be expensive and not freely available
Mixed 5-HT_4 agonists/5-HT_3 antagonists are not more effective than placebo at improving symptoms of IBS-C.	Strong	Low	✓	✓	✓	✓
Linaclotide is superior to placebo for the treatment of IBS-C.	Strong	High	✓	✓	✓	Expensive
Lubiprostone is superior to placebo for the treatment of IBS-C.	Strong	Moderate	✓	✓	✓	Expensive
There is no evidence that polyethylene glycol improves overall symptoms and pain in patients with IBS.	Weak	Very low	Not clear whether this intervention is effective	Not clear whether this intervention is effective, and hence although adverse events are rare, cannot evaluate risks vs. benefits	✓	Can be moderately expensive for patients

GI, gastrointestinal; GRADE, Grading of Recommendations Assessment, Development and Evaluation; 5-HT_3, serotonin subtype 3; 5-HT_4, serotonin subtype 4; IBS, irritable bowel syndrome; IBS-C, IBS with constipation; IBS-D, IBS with diarrhea; NNH, number needed to harm; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

[a]Cost was classified as expensive for the health service if the listed medication cost was >$5 per day. At this level, an economic analysis (289) has shown there is less certainty that the drug is cost effective, although it is important to emphasize that this will be cost effective for some patients but may not be for those with milder symptoms.

[b]Check marks indicate that the criterion was fulfilled/not a concern.

Table 4. Summary of results of monograph on interventions for CIC

Statement	No. of trials	No. of patients	RR symptoms (95% CI)	NNT (95% CI)	Recommendation	Quality of evidence
Some fiber supplements increase stool frequency in patients with CIC.	3	293	0.25 (0.16–0.37)	2 (1.6–3)	Strong	Low
PEG is effective in increasing stool frequency and improving stool consistency in CIC.	4	573	0.52 (0.41–0.65)	3 (2–4)	Strong	High
Lactulose is effective in increasing stool frequency and improving stool consistency in CIC.	2	148	0.48 (0.27–0.86)	4 (2–7)	Strong	Low
Sodium picosulfate and bisacodyl are effective in CIC.	2	735	0.54 (0.42–0.69)	3 (2–3.5)	Strong	Moderate
Prucalopride is more effective than placebo at improving symptoms of CIC.	8	3,140	0.81 (0.75–0.86)	5 (4–8)	Strong	Moderate
Linaclotide is effective in CIC.	3	1,582	0.84 (0.80–0.87)	6 (5–8)	Strong	High
Lubiprostone is effective in the treatment of CIC.	4	651	0.67 (0.58–0.77)	4 (3–6)	Strong	High
Biofeedback is effective in CIC patients with demonstrated evidence of pelvic floor dyssynergia.	3	216	0.33 (0.22–0.50)	2 (1.6–4)	Weak	Low

CI, confidence interval; CIC, chronic idiopathic constipation; NNT, number needed to treat; PEG, polyethylene glycol; RR, relative risk.

Table 5. Reasons for quality of evidence of assessment of data on CIC according to GRADE criteria

Statement	Quality assessment	Study limitations	Inconsistency	Indirectness of evidence	Imprecision	Reporting bias
Some fiber supplements increase stool frequency in patients with CIC.	Low	All trials were unclear risk of bias but did show a marked effect	End points different even in the studies that could be combined	✓[a]	Only a small number of patients studied	Not evaluable
PEG is effective in increasing stool frequency and improving stool consistency in CIC.	High	All RCTs low risk of bias and demonstrated strong treatment effect	Moderate heterogeneity between studies	✓	✓	Not evaluable
Lactulose is effective in increasing stool frequency and improving stool consistency in CIC.	Low	Both trials at high risk of bias but there was a strong treatment effect	Moderate heterogeneity between studies	✓	Only a small number of patients studied with wide 95% CIs	Not evaluable
Sodium picosulfate and bisacodyl are effective in CIC.	Moderate	Both trials low risk of bias and strong treatment effect	Significant heterogeneity between studies	✓	Modest number of patients studied for each intervention	Not evaluable
Prucalopride is more effective than placebo at improving symptoms of CIC.	Moderate	5/8 Trials were low risk of bias and these studies were also positive	Significant heterogeneity between studies that was unexplained	✓	✓	✓
Linaclotide is effective in CIC.	High	✓	✓	✓	✓	✓
Lubiprostone is effective in the treatment of CIC.	High	Two trials low risk of bias, strong treatment effect	✓	✓	✓	Not evaluable
Biofeedback is effective in CIC patients with demonstrated evidence of pelvic floor dyssynergia.	Low	All three trials were high risk of bias but the treatment effect was marked	End points different even in the studies that could be combined and intervention slightly different between studies	✓	Very modest number of patients studied.	Not evaluable

CI, confidence interval; CIC, chronic idiopathic constipation; GRADE, Grading of Recommendations Assessment, Development and Evaluation; PEG, polyethylene glycol; RCT, randomized controlled trial.
[a]Check marks indicate that the criterion was fulfilled/not a concern.

Table 6. Reasons for strength of recommendation for treatments of CIC according to GRADE criteria

Statement	Recommendation	Quality of evidence	All patient groups	Benefits vs. risks	Patient values	Cost[a]
Some fiber supplements increase stool frequency in patients with CIC.	Strong	Low	✓[b]	Fiber can cause bloating and abdominal discomfort	Some patients do not like taking fiber supplements	✓
PEG is effective in increasing stool frequency and improving stool consistency in CIC.	Strong	High	✓	✓	✓	Can be expensive to patients
Lactulose is effective in increasing stool frequency and improving stool consistency in CIC.	Strong	Low	✓	Lactulose can cause bloating	✓	✓
Sodium picosulfate and bisacodyl are effective in CIC.	Strong	Moderate	✓	✓	✓	✓
Prucalopride is more effective than placebo at improving symptoms of CIC.	Strong	Moderate	✓	✓	✓	Expensive
Linaclotide is effective in CIC.	Strong	High	✓	✓	✓	Expensive
Lubiprostone is effective in the treatment of CIC.	Strong	High	✓	✓	✓	Expensive
Biofeedback is effective in CIC patients with demonstrated evidence of pelvic floor dyssynergia.	Weak	Low	✓	✓	Some patients not receptive to the idea of biofeedback	Expensive

CIC, chronic idiopathic constipation; GRADE, Grading of Recommendations Assessment, Development and Evaluation; PEG, polyethylene glycol.
[a]Cost was classified as expensive for the health service if the listed medication cost was >$5 per day. At this level, an economic analysis (289) has shown there is less certainty that drug is cost effective, although it is important to emphasize that this will be cost effective for some patients but may not be for those with milder symptoms.
[b]Check marks indicate that the criterion was fulfilled/not a concern.

In the largest study to date, 275 patients, of whom 53–58% were IBS-C and 19–29% were IBS-D, were randomized to one of three arms: 10 g of the soluble fiber psyllium, 10 g of the insoluble fiber bran, or 10 g of a placebo once daily for 12 weeks (57). During the first month, a significantly greater proportion of patients receiving psyllium, but not bran, reported adequate symptom relief for at least 2 weeks compared with placebo (57% vs. 35% psyllium vs. placebo; RR 1.60, 95% CI 1.13–2.26). Bran was more effective than placebo during the third month of treatment only (57% vs. 32%; 1.70, 1.12–2.57). After 3 months of treatment, symptom severity in the psyllium group was reduced by 90 points compared with 49 points in the placebo group ($P=0.03$) and 58 points in the bran group ($P=0.61$ vs. placebo). No differences were found with respect to quality of life. Dropout was most common in the bran group; most commonly because of exacerbation in IBS.

Data on overall adverse events were only provided by six trials (57,58,60,64,65,69). These trials evaluated 566 patients, but as numbers of adverse events were so small in 5 of the trials, pooling of data was not carried out. A total of 130 (38.8%) of 335 patients receiving fiber reported adverse events compared with 63 (27.3%) of 231 in the placebo arms.

Summary: Although its use in the management of IBS is time honored, the status of fiber, in general, in IBS, is far from straightforward. Insoluble fibers may exacerbate symptoms and provide little relief; soluble fibers and psyllium, in particular, provide relief in IBS. These latter effects appear to transcend expected benefits in terms of relief of constipation.

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

The suggestion that the gut bacteria could be relevant to IBS first came from the observation that a small, although definite, proportion of individuals who suffer an episode of bacterial gastroenteritis will go on to develop IBS *de novo*; postinfectious IBS (70). Although bacterial fermentation has been linked to bloating and flatulence and changes in the microbiota have been described in IBS, the contribution of the microbiota to these, or other symptoms in IBS, is unclear. Thus, although both small intestinal bacterial overgrowth (SIBO) (71) and quantitative and qualitative changes in the fecal microbiota (72) have also been linked to IBS (73), the overall contribution of SIBO to IBS remains controversial (74), and findings in relation to the microbiota require confirmation in larger patient populations. Prebiotics, probiotics, and prebiotic–probiotic preparations have been used for decades on an empirical basis by IBS sufferers; they have only recently been subjected to scrutiny in clinical trials. The interpretation of probiotic studies in IBS remains challenging as studies have employed different species, strains, preparations, and doses in various patient populations and often in substandard trials.

Although initial studies, employing the lactulose hydrogen breath test, suggested that more than "three quarters" of all IBS sufferers had SIBO (75), subsequent studies have, in general, failed to confirm such a high prevalence of SIBO in IBS (73,74). These divergent results may relate to problems inherent to the lactulose breath hydrogen test that may provide an overestimation of the true positive rate (73). Nevertheless, this finding provided a rationale for assessing antibiotics in IBS. Rifaximin, a nonabsorbable antibiotic, has demonstrated efficacy in clinical trials in IBS-D, and although statistically significant improvements were demonstrated over placebo in global IBS symptoms as well as in bloating, it is important to note that tests for SIBO were not performed in these pivotal trials, leaving the mechanism of action of rifaximin in IBS unclear (76).

(a) Prebiotics and synbiotics in IBS: There is insufficient evidence to recommend prebiotics or synbiotics in IBS.
Recommendation: weak. Quality of evidence: very low.

(b) Probiotics in IBS: Taken as a whole, probiotics improve global symptoms, bloating, and flatulence in IBS.
Recommendations regarding individual species, preparations, or strains cannot be made at this time because of insufficient and conflicting data.
Recommendation: weak. Quality of evidence: low.

(c) Antibiotics in IBS: The poorly absorbable antibiotic rifaximin is effective at reducing total IBS symptoms and bloating in diarrhea-predominant IBS.
Recommendation: weak. Quality of evidence: moderate.

We identified one RCT that evaluated the *prebiotic* transgalactooligosaccharide in IBS (77); this study was excluded from further analysis as the data were not extractable. In relation to probiotics, it should be noted that changes in diet and intake of dietary fiber can exert prebiotic effects on gut microbiota; these are addressed in previous sections. We identified two trials assessing 198 IBS patients that evaluated *synbiotics* vs. control preparations. (78,79) Both studies evaluated different products. We excluded two other RCTs of synbiotics in IBS as data were not extractable in one case, (80) and in the second there was no control arm (81).

There was one study that assessed dichotomous outcomes in 68 patients (79). 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 ($P < 0.01$). Both trials (78,79) assessed global IBS symptoms on a continuous scale in 185 patients; there was no statistically significant effect of synbiotics in reducing IBS symptom scores, even though both trials were individually positive, again because of significant heterogeneity.

We updated our previous systematic review and meta-analysis on *probiotics* in IBS (22,82), and identified a total of 20 new trials (83–102). However, one of these was a full publication of a trial previously included in the original meta-analysis in abstract form (89,103), and one trial in the original meta-analysis was pseudorandomized and included acupuncture in both study arms (104), and hence we excluded these two studies (103,104). Therefore, in total, there were 35 RCTs (83–102,105–119), involving 3,452 patients. Fourteen trials were at low risk of bias (87,89,91–93,97,99,101,105,109–111,118,119), with the remainder being unclear.

There were 23 RCTs involving 2,575 patients (as reported on **Table 1**) that gave outcomes as a dichotomous variable. Probiotics were statistically significantly better than placebo (RR of IBS not improving = 0.79, 95% CI 0.70–0.89), with the NNT of 7 (95% CI 4–12.5). There was statistically significant heterogeneity between studies. A further complicating factor in the assessment of probiotics was the use of a great variety of preparations. Combination probiotics, as well as formulations based on specific species (but widely variable strains); *Lactobacillus*, *Bifidobacterium*, *Escherichia*, and *Streptococcus*, were assessed in individual trials. Subanalysis only demonstrated a significant effect for combination probiotics, *Lactobacillus plantarum DSM* 9843 and *E. coli* DSM17252, but there was significant heterogeneity between studies for the first two and only one study for the third.

There were 24 trials, making 25 comparisons, and assessing 2001 patients who reported improvement in global IBS symptom scores or abdominal pain scores. There was a statistically significant effect of probiotics in reducing symptoms with no significant heterogeneity. Subanalysis, on this occasion, revealed significant effects for combinations of probiotics, but not for those containing *Lactobacillus* spp., *Bifidobacterium* spp., or *Saccharomyces* spp.

There were 17 separate trials, making 18 comparisons and containing 1,446 patients, that reported the effect of probiotics on bloating symptom scores. Overall, bloating scores were significantly reduced with probiotics, but with significant heterogeneity between individual study results.

In the 10 trials that assessed this outcome, flatulence scores were significantly lower with probiotics compared with placebo with no significant heterogeneity detected.

There was no apparent benefit detected for probiotics on urgency in the six trials that assessed this symptom.

Total adverse events were reported by 24 RCTs containing 2,407 patients. Overall, 201 (16.5%) of 1,215 patients allocated to probiotics experienced any adverse event compared with 164 (13.8%) of 1,192 assigned to placebo with the NNH of 35 (95% CI 16–362).

We identified 6 RCTs (120–124) involving 1,916 participants that evaluated *antibiotic* therapy in IBS patients. Two trials evaluating metronidazole (125) and rifaximin (126) were excluded as they did not provide extractable data. A further RCT (127) assessed *Helicobacter pylori* eradication therapy but was excluded as it assessed symptoms 2 years after a 1-week course of antibiotics. Overall, antibiotic therapy improved IBS symptoms compared with placebo, with no significant heterogeneity between studies. One trial (124) evaluated neomycin in 111 patients with a significant effect in favor of neomycin (RR = 0.73, 95% CI 0.56–0.96) with the NNT of 5 (95% CI 3–33). The remaining 5 trials (120–123) evaluated rifaximin in 1,805 IBS patients. There was a statistically significant benefit in favor of the anti-

biotic (RR = 0.84, 95% CI 0.78–0.90) with the NNT of 9 (95% CI 6–12.5). There were three (122,123) low risk of bias trials assessing 1,330 patients.

Three RCTs reported adverse events (121,122,124) in 1,456 patients. There was no difference in overall adverse events between the antibiotic and placebo groups (RR of adverse events = 0.70, 95% CI 0.42–1.16).

Summary: Although data accumulate to suggest a role for the microbiota in IBS, the primacy of any reported changes in enteric populations in the pathogenesis of IBS remains to be confirmed. Although, at this time there is insufficient evidence to permit a recommendation on the use of prebiotics or synbiotics in IBS, aggregated data do indicate a beneficial effect for probiotics, with bloating and flatulence appearing to be especially responsive. Though recognizing the intrinsic differences that exist between individual probiotic strains and the consumer's desire to obtain guidance on product selection, limitations intrinsic to available data, as well as a lack of comparative studies, severely limit one's ability to recommend a particular strain or product at this time. The antibiotic rifaximin, although not approved for this indication by the Food and Drug Administration, has shown modest but consistent efficacy in nonconstipated IBS and seems to be well tolerated and, despite concerns regarding the long-term or repeated use of an antibiotic, has proven safe at least over the time periods in which it has been evaluated.

4. Antispasmodics in IBS

Antispasmodics have been used for decades on an empirical basis in the treatment of IBS based on the assumption that gut, and especially colonic smooth muscle spasm, contributes to IBS symptoms and pain in particular; hence, the term *spastic colon*.

Certain antispasmodics (otilonium, hyoscine, cimetropium, pinaverium, and dicyclomine) provide symptomatic short-term relief in IBS. Adverse events are more common with antispasmodics than placebo.

Recommendation: weak. Quality of evidence: low.

We identified 23 RCTs (60,64,67,128–147) evaluating 2,154 patients with IBS. There was considerable variation between the studies concerning diagnostic and inclusion criteria, dosing schedule, and study end points. Only 3 studies used standardized diagnostic criteria (Rome I or II) (131,138,140), whereas all other 20 studies used author-defined IBS, reflecting the fact that most trials were conducted before Rome definitions were published. The majority of trials did not differentiate between the types of IBS patients recruited. Overall, the quality of trials was poor, with only 4 recruiting more than 100 patients. Only four trials (67,131,133,144) reported an adequate method of randomization and none reported on concealment of allocation, although all were double blind. Risk of bias was unclear in all of the trials. Of the drugs used in the various studies, only hyoscine (64,67,146) and dicyclomine (142) are available in the United States.

This review shows that as a class, antispasmodic therapy has a statistically significant effect in improving IBS symptoms with the NNT of 5 (95% CI 4–9). However, the effect of individual antispasmodics is variable and difficult to interpret, as there are only a small number of studies evaluating each of the 12 different drugs available for review.

With respect to individual agents, otilonium (128,129,131, 132,138), hyoscine bromide (64,67,146), cimetropium bromide (130,134,143), pinaverium bromide (133,139,147), and dicyclomine hydrochloride (142) showed beneficial effects with NNTs of 5, 3, 3, 3, and 4, respectively. However, some of these were evaluated in as few as just one study (142), and for those that were assessed in multiple studies, heterogeneity was a problem in some instances.

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 numbers of patients studied were small.

Fifteen trials included in this review reported adverse events with either active drug or placebo. In total, 144 (16.3%) of 883 patients assigned to antispasmodics experienced adverse events compared with 92 (10.4%) of 882 allocated to placebo. When data were pooled, the incidence of adverse events was significantly higher among those taking antispasmodics as compared with placebo (RR of experiencing any adverse event = 1.61; 95% CI 1.08–2.39), with the NNH of 20 (95% CI 9.5–333). The most common 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.

Summary: Although many of the relevant clinical trials are old and far from ideal in terms of quality, antispasmodics, as a category, are effective in IBS, though their use may be limited by anticholinergic adverse events. However, not all antispasmodics have been shown to be effective, and studies on individual agents vary in quality and outcome measures. Furthermore, the availability of some of the more effective agents may be limited to certain regions.

5. Peppermint oil in IBS

Peppermint oil can be found in various preparations available through conventional or complementary venues. Limited experimental data suggest that it can relax smooth muscle, but it may also have effects via attenuation of visceral hypersensitivity and modulation of pain sensation, and hence its use for the treatment of IBS.

Peppermint oil is superior to placebo in improving IBS symptoms. The risk of adverse events is no greater with peppermint oil than with placebo.

Recommendation: weak. Quality of evidence: moderate.

We identified five RCTs (148–152) involving 482 patients. Most trials did not differentiate between the types of IBS patients recruited, with only one study providing data on this (148). There was only one RCT at low risk of bias (152), with the remainder being unclear. This RCT reported a less dramatic effect of peppermint oil on IBS symptoms compared with placebo, but this was

still statistically significant. Overall, there was a statistically significant effect in favor of peppermint oil compared with placebo with the NNT of 3 (95% CI 2–4). However, there was significant heterogeneity between results. In these studies, an enteric-coated preparation of peppermint oil was employed in doses ranging from 187 to 225 mg t.i.d.

When data were pooled, the incidence of adverse events was not significantly higher among those taking peppermint oil as compared with placebo (RR of experiencing any adverse event = 1.26, 95% CI 0.75–2.12).

Summary: In specific formulations, which may not be universally available, peppermint oil is effective in IBS.

6. Loperamide in IBS

There is insufficient evidence to recommend loperamide for use in IBS.

Recommendation: strong. Quality of evidence: very low.

There were two RCTs (153,154) involving 42 patients. There was no statistically significant effect in favor of loperamide compared with placebo. Both trials stated the type of IBS patients recruited, with one study recruiting only IBS-M patients (153) and the other only IBS-D (154).

Data on overall adverse events were provided in both trials. There were no adverse events in either arm in one trial (153) and four adverse events in each arm of the other study (154).

Summary: Although loperamide is an effective antidiarrheal, there is no evidence to support the use of loperamide for relief of global symptoms in IBS.

7. Antidepressants in IBS

Antidepressants were first introduced into the management of IBS based on the observation that depression and anxiety were frequent comorbidities among IBS subjects seen in secondary and tertiary care. Subsequent studies suggested that in subdepression doses these agents were effective in relieving pain of visceral origin.

Antidepressants (tricyclic antidepressants and selective serotonin reuptake inhibitors) are effective in symptom relief in IBS.

Side effects are common and may limit patient tolerance.

Recommendation: weak. Quality of evidence: high.

We updated our previous systematic review and meta-analysis on antidepressants in IBS (20) and identified four further papers (155). Overall, there were 17 RCTs (64,156–171) evaluating 1,084 patients. The majority of trials did not differentiate between the type of IBS patients recruited, with seven studies providing data on this (159,161,162,164–166,170), one of which recruited only IBS-C patients (164) and another only IBS-D patients (165). Only three of the RCTs were at low risk of bias (167,169,170), with the remainder being unclear.

Antidepressants were effective in treating IBS symptoms with the NNT of 4 (95% CI 3–6). The effect of antidepressant therapy on abdominal pain was reported by 7 RCTs (158,159,161, 164–166,169), with 87 (46.7%) of 182 patients receiving antidepressants having persistent abdominal pain following treatment as compared with 123 (72.8%) of 169 subjects allocated to placebo, giving a RR of abdominal pain persisting of 0.62 (95% CI 0.43–0.88), but with considerable heterogeneity between studies ($I^2 = 72.4\%$, $P = 0.001$).

Tricyclic antidepressants were studied in 11 RCTs involving 744 patients (64,156–158,160,163,165–169), and active therapy was associated with a reduction in IBS symptoms compared with placebo with the NNT of 4. Selective serotonin reuptake inhibitors were studied in 7 RCTs involving 356 patients (159,161–164, 170,171), and active therapy was associated with a reduction in IBS symptoms compared with placebo with the NNT of 4.

Only seven trials reported on overall adverse events vs. placebo (157–160,162,166,168). In total, 65 (31.3%) of 208 patients assigned to antidepressants experienced adverse events as compared with 33 (16.5%) of 200 allocated to placebo. When data were pooled, the incidence of adverse events was significantly higher among those taking antidepressants as compared with placebo (RR of experiencing any adverse event = 1.63, 95% CI 1.18–2.25). The NNH was 9 (95% CI 5–111). Drowsiness and dry mouth were more common in patients taking tricyclic antidepressants than those on placebo.

Summary: Both tricyclic antidepressants and selective serotonin reuptake inhibitors are effective in providing global symptom relief and reducing pain in IBS. Adverse events and patient, as well as physician, acceptability have limited their use and influenced our recommendation. Available data, other than adverse event profile (e.g., constipating effects of tricyclic antidepressants), do not permit guidance on patient selection for antidepressant therapy.

8. Psychological therapies, including hypnotherapy, in IBS

A variety of psychological interventions are effective in improving IBS symptoms.

Recommendation: weak. Quality of evidence: very low.

We updated our previous systematic review and meta-analysis on psychological therapies in IBS (20,155), and identified a total of 10 new papers containing 11 separate RCTs, thereby providing in total 30 papers reporting 32 separate trials, involving 2,189 patients (167,172–200). The quality of these trials was generally poor, with only 8 having a sample size of more than 100 (167,174,175,178,18 1,189,191,194). Because of the nature of the intervention, double-blind studies would not have been possible, but only four papers reported that investigators were blinded (167,174,175,192). All of the trials were at high risk of bias.

There was a statistically significant effect in favor of psychological therapies with the NNT of 4 (95% CI 3–5), but with significant heterogeneity between studies.

In terms of the 10 different types of psychological therapies evaluated, the benefits were demonstrated for cognitive behavioral therapy (NNT of 3 (95% CI 2–6)), hypnotherapy (NNT of 4 (95% CI 3–8), multi-component psychological therapy (NNT of 4 (95% CI 3–7)), multi-component psychological therapy administered via the telephone (NNT of 5 (95% CI 3–17)), and

dynamic psychotherapy (NNT of 3.5 (95% CI 2–25)). No significant effects were evident for relaxation therapy, self-administered cognitive behavioral therapy, behavioral therapy delivered via the internet, stress management, or mindfulness meditation training. However, the latter three have only been tested in one or two RCTs, and therefore a definite lack of benefit cannot be assumed. Only four trials (172,178,184,187) used "sham" or "control" psychological interventions as a comparison.

Adverse events data were poorly reported by individual RCTs, precluding any meaningful analysis.

Summary: Although issues relating to blinding and choice of control intervention have complicated their evaluation, a variety of therapeutic approaches, loosely aggregated under the term "psychological therapies," have been shown to be effective in IBS. Availability of skilled therapists experienced in the management of IBS greatly limits their use.

9. Serotonergic agents

Serotonin (5-hydroxytryptamine (5-HT)) plays a critical role in gastrointestinal secretion, motility, and sensation (201), and a variety of 5-HT receptors have been targets for new drug development in functional gastrointestinal disorders (202). The serotonin subtype 3 (5-HT_3) receptors have been shown to play an important role in visceral pain, and 5-HT_3 antagonists decrease painful sensations from the gut and slow intestinal transit (203,204). Alosetron, a selective 5-HT_3 antagonist, was therefore evaluated in diarrhea-predominant IBS and, although it showed efficacy, instances of severe constipation and ischemic colitis (205) led, initially, to its withdrawal by the US Food and Drug Administration (FDA). It was subsequently reintroduced by the FDA in a restricted manner under a risk management plan for "women suffering with severe diarrhea-predominant IBS that is disabling" (http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM227960.pdf; accessed June 10th 2014). The risk management plan was converted to a risk evaluation and mitigation strategy in 2010. Other 5-HT_3 antagonists such as cilansetron and ramosetron have never been introduced into clinical practice.

The serotonin subtype 4 (5-HT_4) receptors are distributed throughout the gastrointestinal tract and stimulation of these receptors enhances intestinal secretion, augments the peristaltic reflex, and increases gastrointestinal transit (206,207). Tegaserod is an aminoguanidine-indole categorized as a partial, selective 5-HT_4 agonist. The FDA granted approval for the use of tegaserod in women with IBS with constipation in July 2002. Because of possible cardiovascular adverse effects, tegaserod was withdrawn from the US market in March 2007. Tegaserod is the only 5-HT_4 partial agonist that has been evaluated in large, prospective, randomized controlled studies in IBS patients. As tegaserod is no longer available in the United States, an updated analysis of tegaserod efficacy and safety has not been performed. The interested reader is referred to the previous systematic review (19). A number of selective 5-HT_4 agonists have been developed and have shown efficacy in constipation (e.g., prucalopride that is available in Canada and the European Union) but no data are, as yet, available on the efficacy or safety of these agents for the treatment of IBS.

(a) 5-HT_3 antagonists in IBS: Alosteron is effective in females with diarrhea-predominant IBS.
Recommendation: weak. Quality of evidence: moderate.

We updated our previous systematic review and meta-analysis (19) and identified two new studies providing a total of 13 trials eligible containing 8,173 patients for inclusion (208–220). Only one trial was at low risk of bias (216), with the remainder unclear. All but one recruited nonconstipated IBS. Most trials recruited women only, or predominantly women, with the exception of two Japanese studies where men predominated (218,219), and a US-based trial that recruited only men (213).

Overall, there was a statistically significant effect in favor of 5-HT_3 antagonists with the NNT of 7 and significant heterogeneity.

There appeared to be no difference in efficacy between the three drugs alosetron (208,210–214,216), cilansetron (209,215,220), and ramosetron (218,219) within this class, all proving effective with NNTs of 8, 6, and 7, respectively.

There were 9 studies (208,210–214,216,218,219) evaluating 5,564 patients that provided total adverse event data. 5-HT_3 antagonists had statistically significantly more adverse events than placebo (RR of any adverse event = 1.17, 95% CI 1.08–1.25). The NNH was 11 (95% CI 8–17). The main adverse event that was more common with 5-HT_3 antagonists than with placebo was constipation. Ischemic colitis has been reported with alosetron, and it was withdrawn by the FDA in November 2001. In June 2002, the FDA announced the approval of a supplemental New Drug Application that allowed restricted marketing of alosetron to treat only women with severe diarrhea-predominant IBS. The approval includes a risk management program (termed a risk evaluation and mitigation strategy since 2010) to ensure patients and physicians are fully informed of the theoretical risks and possible benefits of alosetron (221).

(b) 5-HT4 agonists in IBS: No further analysis of these agents was performed as there were no new data and tegaserod has been withdrawn in most areas.

(c) Mixed 5-HT3 antagonists/5-HT4 agonists: Mixed 5-HT_4 agonists/5-HT_3 antagonists are not more effective than placebo at improving symptoms of constipation-predominant IBS.
Recommendation: strong. Quality of evidence: low.

The complex physiology involved in the generation of IBS symptoms is thought to represent an intricate balance of 5-HT receptor agonism and antagonism (201,206,207). Several agents classified as mixed 5-HT_3 antagonists/5-HT_4 agonists have been developed for the treatment of IBS. These are collectively and individually reviewed below. It should be noted that cisapride has not been widely available since withdrawal from the US market in July 2000 and that this drug was shown to be not more effective than placebo in a recent meta-analysis (19).

A total of 9 double-blind, placebo-controlled trials involving 2,905 patients were eligible for inclusion (222–230). Four

studies each involved cisapride (223,225,227,228) or renzapride (222,224,226,229); one study involved mosapride (230). Eight trials recruited patients with constipation-predominant IBS (222–225,227–230) and one mixed IBS (226). The methodological quality of trials was low.

Analysis of all nine studies revealed no statistically significant differences between placebo and mixed 5-HT_3 antagonists/5-HT_4 agonists for the treatment of IBS and significant heterogeneity was identified between studies.

In terms of individual agents, neither renzapride (222,224,226, 229) in constipation-predominant or mixed IBS nor mosapride (230) showed significant benefit over placebo.

There was no statistically significant increase in adverse events with mixed 5-HT_3 antagonists/5-HT_4 agonists as compared with placebo.

Summary: Of the various agonists and antagonists to serotonergic receptors that have been developed and evaluated in IBS, only alosetron and ramosetron, both 5-HT_3 antagonists, are available (although in certain regions only) and supported by evidence of efficacy. Because of concerns regarding adverse events, the use of alosetron in the United States is limited to women with severe diarrhea-predominant IBS and can be prescribed only in the context of a carefully monitored program. Ramosetron is approved for the management of diarrhea-predominant IBS in Japan, Korea, and Thailand.

10. Prosecretory agents
(a) Linaclotide: Linaclotide is superior to placebo for the treatment of constipation-predominant IBS.
Recommendation: strong. Quality of evidence: high.

Linaclotide is a 14-amino acid peptide structurally similar to hormones in the guanylin peptide family. Guanylin peptides are endogenous hormones that assist in the regulation of intestinal fluid and electrolyte homeostasis by binding to, and activating, guanylate cyclase-C receptors on the lumen of intestinal epithelium. Activation of guanylate cyclase-C results in an increase of cyclic guanosine monophosphate that triggers a series of events leading to the activation of the cystic fibrosis transmembrane conductance regulator that results in secretion of bicarbonate and chloride into the lumen, followed by sodium and water flux into the intestinal lumen, as well as modulation of pain afferent sensors (231).

Three randomized clinical trials in IBS patients were identified involving 2,028 combined patients (232–234). All trials were at low risk of bias, and there was no significant heterogeneity between individual trial results.

There was a statistically significant effect in favor of linaclotide compared with placebo with the NNT of 6 (95% CI 5–8), with no significant heterogeneity between studies. There was a statistically significant effect in favor of linaclotide compared with placebo on abdominal pain (NNT of 8), but with significant heterogeneity between individual trial results.

Data on overall adverse events were provided by two of the three trials (232,234). Overall, adverse event rates were not higher among those taking linaclotide compared with placebo (RR = 1.09, 95% CI 0.96–1.24). However, diarrhea, reported in all three trials, was significantly more likely with linaclotide as compared with placebo (RR = 6.62, 95% CI 4.39–9.96) with the NNH of 6 (95% CI 5.5–8). Flatulence, reported in two trials (232,234), was also significantly more common with active therapy (RR = 2.27, 95% CI 1.18–4.36), with the NNH of 50 (95% CI 23–167).

(b) Lubiprostone: Lubiprostone is superior to placebo for the treatment of constipation-predominant IBS.
Recommendation: strong. Quality of evidence: moderate.

Lubiprostone activates the chloride channel type 2 (CIC-2) on the apical surface of the intestinal epithelium. This results in chloride and water flux into the intestinal lumen, resulting in faster transit through the small and large intestines.

Four clinical trials of lubiprostone in IBS patients have been reported in three separate papers (235–237). However, one of these was a mixed population of IBS and CIC patients (236). Three studies reported dichotomous data in 1,366 IBS patients (235,237). All trials were at low risk of bias. There was a statistically significant effect in favor of lubiprostone as compared with placebo, with the NNT of 12.5 (95% CI 8–25), and no significant heterogeneity between the three individual trial results. The quality of evidence was graded as moderate according to GRADE criteria, as the effect on overall IBS symptoms was modest and the 95% CI for the RR was relatively close to a null effect. Furthermore, dichotomous data for IBS patients from one trial were not available (236).

Data on overall adverse events were reported in all three trials, but pooled for the two trials reported in a single paper (235). In the study by Johanson *et al.* (237), adverse events were reported by 66% of lubiprostone patients as compared with 58% of placebo, but this difference was not statistically significant. Nausea was also commoner (17% with lubiprostone compared with 4% with placebo), but again this was not statistically significant. The only adverse event occurring more frequently among those receiving lubiprostone was diarrhea (NNH = 10, 95% CI 5–25). In the two studies that pooled adverse events data (235), 50% and 51% of IBS patients receiving lubiprostone and placebo, respectively, reported at least one adverse event. Diarrhea occurred in 6% of lubiprostone-treated patients compared with 4% of those receiving placebo. Nausea was reported by 8% of those allocated to lubiprostone compared with 4% of those assigned to placebo.

Summary: The prosecretory agents linaclotide and lubiprostone are effective in constipation-predominant IBS. As both of these agents were evaluated in comparison with placebo rather than "standard therapy," their position in an IBS treatment algorithm (i.e., for those who have failed other treatments or as primary therapy) is difficult to define and complicated by lack of consensus on what "standard" therapy should be in IBS, given the limitations of data on other agents.

11. PEG in IBS
There is no evidence that PEG improves overall symptoms and pain in patients with IBS.
Recommendation: weak. Quality of evidence: very low.

PEG is a large polymer that behaves as an osmotic laxative, and although it is approved by the FDA for the treatment of occasional constipation, it has not been extensively studied in patients with IBS-C. One open-label study in 27 adolescents with IBS-C suggested that PEG improved stool frequency but not pain (238). We identified only two RCTs (239,240) of PEG in IBS. In one trial, there was no statistically significant effect on bowel movements or discomfort and pain (239). In the second trial (240), which recruited 139 patients with IBS with constipation, the mean increase in spontaneous bowel movements was significantly greater with PEG compared with placebo at 4 weeks, but there was no difference in effect on abdominal pain or discomfort. Response rates, defined as more than four spontaneous bowel movements per week with an increase of two or more from baseline and no worsening of abdominal pain or discomfort, were significantly higher with PEG (36.5% vs. 17.5% with placebo, $P<0.05$). However, there was no significant difference in the proportion of patients with a pain response, defined as a decrease by 10% or more from baseline (61.9% vs. 47.6%, $P>0.1$). Adverse event rates were higher with PEG (38.8% vs. 32.9%), but most of these were mild or moderate.

Summary: There is no evidence that PEG formulations alleviate pain or provide overall symptom relief in IBS.

Chronic idiopathic constipation

1. Fiber in CIC

Some medicinal and dietary fiber supplements increase stool frequency in patients with chronic idiopathic constipation.
Recommendation: strong. Quality of evidence: low.

Dietary fiber is defined as carbohydrate polymers that are incapable of being digested in the normal small intestine and are delivered to the colon. Fiber can be part of ingested food or purified and taken as a supplement ("medicinal fiber"). Fiber is classified as "soluble" or "insoluble" depending on its interaction with water. Psyllium is the archetypical soluble fiber; bran is insoluble.

Psyllium husk is the outer coat of the psyllium seed (known in India as ispaghula seed) from the plant *Plantago ovata*. It can undergo bacterial fermentation in the colon, thereby producing gas and bloating. Semisynthetic bulking agents less susceptible to fermentation include calcium polycarbophil and methylcellulose. Few studies have been done with bulking agents in CIC and the quality of evidence about the use of these agents is very low.

Six trials met the criteria for inclusion in this review (241–246), but a formal meta-analysis was only possible with three trials (243,245,246), and the remaining studies could not be analyzed because of crossover design (241,242) or a failure to provide dichotomous data for extraction (244) with uncertainty regarding whether the study was truly random. Four of the eligible trials used soluble fiber: three used psyllium (241,243,246) and the fourth used a combination of inulin and maltodextrose (245). Two used insoluble fiber: wheat bran in one study (242) and rye bread in the other (244).

Combined data from the three trials (243,245,246) suggested that fiber was beneficial compared with placebo with the NNT of 2 (95% CI 1.6–3) and no statistically significant heterogeneity between studies. Although these trials could be combined for analysis, the definitions of improvement were all different, and in one trial (245) not all patients enrolled in the trial had the outcome that was used to define treatment success present at baseline. The effect size given in this meta-analysis therefore needs to be treated with extreme caution.

In terms of individual formulations, among the three trials (241,243,246) that studied psyllium, including the largest identified RCT conducted by Fenn *et al.* (243), although outcomes varied between these RCTs, all reported significant benefits with psyllium.

Lopez Roman *et al.* (245) used 20 g of a soluble fiber mixture of inulin and maltodextrin, administered as a dairy preparation, and reported significant reductions in the proportion of patients with straining during defecation, sensation of incomplete evacuation, or sensation of obstruction with soluble fiber. In addition, the number of days between bowel movements was also significantly reduced.

Two trials reported on the efficacy of insoluble fiber in CIC (242,244). The 24 patients recruited were allocated to receive 20 g of bran per day or placebo. No significant benefits were noted with bran (242) but rye bread was effective (244).

No single study reported total adverse events. One trial reported the number of patients in each trial arm who dropped out because of adverse events (one with psyllium and two with placebo) (243). Ashraf *et al.* (241) recorded individual adverse events, with 18% of psyllium patients experiencing abdominal pain compared with 0% of placebo patients, but no differences in back pain, bloating, or cramping. Finally, there were higher combined symptom scores for gastrointestinal side effects such as abdominal pain, flatulence, borborygmi, and bloating with rye bread compared with low-fiber toast (244).

Summary: Fiber and soluble fiber, in particular, are effective in the management of chronic constipation. Adverse events and bloating, distension, flatulence, and cramping may limit the use of insoluble fiber, especially if increases in fiber intake are not introduced gradually.

2. Osmotic and stimulant laxatives in CIC

Osmotic laxatives contain poorly absorbed ions or molecules that retain water in the intestinal lumen. Osmotic agents used with some frequency include polyethylene glycol, lactulose, magnesium hydroxide, magnesium citrate, magnesium sulfate, and sodium phosphate.

(a) Osmotic laxatives in CIC: PEG is effective in improving symptoms of CIC.
Recommendation: strong. Quality of evidence: high.
Lactulose is effective in improving symptoms of CIC.
Recommendation: strong. Quality of evidence: low.

Five studies compared PEG with placebo (247–251); four reported dichotomous data in 573 patients (247–250) with the

NNT of 3 (95% CI 2–4). All trials were at low risk of bias and there was moderate heterogeneity between studies. Two studies (252,253) evaluated lactulose compared with placebo in 148 patients, with the NNT of 4 (95% CI 2–7). Both trials were at high risk of bias and there was moderate heterogeneity between studies.

Trials with osmotic laxatives did not report on the total number of adverse events. Where reported (247,248), the incidence of individual adverse events, including abdominal pain, or headache, did not differ between active agent and placebo.

(b) Stimulant laxatives in CIC: Sodium picosulfate and bisacodyl are effective in CIC.
Recommendation: strong. Quality of evidence: moderate.

Stimulant laxatives appear to induce fluid and electrolyte secretion by the colon or induce peristalsis in the colon, thereby producing a bowel movement. Stimulant laxatives include senna, bisacodyl, castor oil, cascara, rhubarb, and aloe.

Both trials of stimulant laxatives, containing 735 patients, reported dichotomous data and had a low risk of bias (254,255). In total, 42.1% of all patients randomized to stimulant laxatives failed to respond to therapy as compared with 78.0% of those receiving placebo, with the NNT of 3 (95% CI 2–3.5) and with statistically significant heterogeneity between studies.

Only one RCT reported total numbers of adverse events (254); the RR of experiencing any adverse event with laxatives was 1.94 (95% CI 1.52–2.47, NNH = 3, 95% CI 2–4). Diarrhea occurred significantly more frequently in the two trials (RR = 13.75, 95% CI 2.82–67.14, NNH = 3, 95% CI 2–6) (254,255).

Summary: Although supported by varying levels of evidence, the osmotic laxatives PEG and lactulose and the stimulant laxatives sodium picosulfate and bisacodyl have been shown to be effective in chronic constipation. Other stimulant laxatives, although commonly used by sufferers, have not been adequately studied and cannot be recommended at this time. Other laxatives have not been formally tested.

3. 5-HT_4 agonists in CIC
Prucalopride is more effective than placebo in improving symptoms of CIC.
Recommendation: strong. Quality of evidence: moderate.

Serotonin (5-HT) plays a critical role in the gastrointestinal tract and influences secretory, motor, and sensory functions (256). There are seven major classes of serotonin receptor subtypes (5-HT_{1-7}); stimulation of the 5-HT_4 receptor enhances intestinal secretion, augments the peristaltic reflex, and increases gastrointestinal transit (206,207). The 5-HT_4 receptor agonism has the potential to improve symptoms of CIC. The selective 5-HT_4 agonists prucalopride and velusetrag are reviewed below. Tegaserod, a selective, partial 5-HT_4 agonist, was removed from the US market in March 2007 because of possible adverse cardiovascular effects, and will not be discussed further.

Efficacy: We identified 9 randomized, placebo-controlled trials of 5-HT_4 agonists in CIC involving 3,441 patients (257–265). Eight of these trials involved prucalopride (257–259,261–265), whereas one trial involved velusetrag (260). Two studies investigated the effects of prucalopride in patients either resistant to, or dissatisfied with, laxatives (258,264). One study investigated the effects of prucalopride in patients aged 65 years and older (262). Doses ranged from 0.5 to 4 mg daily; studies lasted from 4 to 12 weeks. Five trials were considered to be at low risk of bias (257,260,262,263,265).

In an analysis of all 9 trials, 72.3% of patients (1,691/2,339) who received 5-HT_4 agonists failed to respond to therapy as compared with 88.1% (1,059/1,202) of those allocated to placebo, with the NNT of 6 (95% CI 5–8). Significant heterogeneity was noted between the studies.

Analysis of the 8 prucalopride trials revealed that 71.1% (1,454/2,045) of patients treated with prucalopride failed to respond to therapy as compared with 87.4% (957/1,095) of those randomized to placebo, with the NNT of 5 (95% CI 4–8). Significant heterogeneity was identified between studies. One study performed a subgroup analysis of those patients treated with prucalopride who had previously failed laxatives (264). The authors reported that the effects of prucalopride were similar in patients who had failed other laxatives compared with the overall population, although a better comparator would have contrasted those patients who did not use laxatives before being enrolled in the trial with those who did.

Analysis of the one velusetrag trial revealed that 80.6% (237/294) of patients treated with velusetrag failed to respond to therapy as compared with 95.3% (102/107) of those randomized to placebo; the NNT was 7 (95% CI 5–11).

Eight trials reported total numbers of adverse events (257–260, 262–265); these were more common in patients treated with 5-HT_4 agonists than with placebo (RR = 1.28, 95% CI 1.11–1.48, NNH = 8; 95% CI 5–16). Individual adverse events including headache, nausea, and diarrhea were all more common in patients who used 5-HT_4 agonists compared with placebo. Selective 5-HT_4 agonists were not associated with an increase in serious adverse event rates (RR = 0.84, 95% CI 0.57–1.25), and only 2 cardiovascular events were reported (supraventricular tachycardia in one patient and electrocardiogram signs of myocardial ischemia in the second) (257,265).

Summary: The 5-HT_4 agonists prucalopride and velusetrag are effective in CIC, with the former supported by considerably more data. To date, the cardiac adverse events that bedeviled prior 5-HT_4 agonists have not emerged as a significant issue; neither is available in the United States at this time.

4. Prosecretory agents in CIC
(a) Linaclotide: Linaclotide is effective in chronic idiopathic constipation. It is generally safe, with the main adverse event being diarrhea.
Recommendation: strong. Quality of evidence: high.

Review of the literature demonstrated no new randomized clinical trials since a previously published systematic review and meta-analysis (21). In total, three trials have been reported

in two separate publications (266,267) involving a total of 1,582 CIC patients. All three trials were at low risk of bias. Overall, 860 (79.0%) of 1,089 patients receiving linaclotide failed to respond to therapy as compared with 468 (94.9%) of 493 placebo patients, with the NNT of 6 (95% CI 5–8). No significant heterogeneity was observed between studies.

Two of the trials pooled adverse events data together (267), precluding meta-analysis. Overall, 58% of linaclotide patients experienced any adverse event compared with 52% of placebo patients. In the third trial, adverse event rates were very similar in number in both treatment arms (33.6% linaclotide vs. 31.9% placebo) (266). Separate adverse events data for diarrhea in each trial were obtained from the authors as part of the meta-analysis (21). Diarrhea was more common in patients receiving linaclotide compared with placebo (RR = 3.08, 95% CI 1.27–7.48, NNH = 12; 95% CI 7–38.5).

(b) Lubiprostone: Lubiprostone is effective in the treatment of chronic idiopathic constipation.
Recommendation: strong. Quality of evidence: high.

We updated a previous meta-analysis on lubiprostone in CIC (21) that had involved three trials of lubiprostone in CIC (268–270). We found two additional clinical trials of lubiprostone (236,271) but these two studies did not provide extractable dichotomous data. After contact with the authors, we obtained dichotomous data for one of these studies (271) but not the second (236), despite contacting both the original authors and the manufacturers. Therefore, this meta-analysis included four trials of lubiprostone in CIC involving 651 patients in total. Two trials were at low risk of bias (270,271).

Of the 364 patients receiving lubiprostone, 45.3% failed to respond to therapy compared with 66.9% of 287 placebo patients, with the NNT of 4 (95% CI 3–6) and no heterogeneity between studies.

Three trials reported adverse events data (268–270). Total numbers of adverse events were significantly higher with lubiprostone (RR = 1.79, 95% CI 1.21–2.65, NNH = 4, 95% CI 3–6). Diarrhea and nausea both occurred significantly more frequently with lubiprostone, but no significant difference in rates of abdominal pain or headache were detected.

Summary: The prosecretory agents linaclotide and lubiprostone are effective in CIC and are well tolerated. There have been no comparative studies. As both were evaluated in comparison with placebo rather than "standard therapy," a recommendation regarding their precise position in a CIC treatment algorithm (i.e., for those who have failed fiber, osmotic, or stimulant laxatives, or as primary therapy) cannot be made at this time.

5. Biofeedback in CIC

One of the potential causes of constipation is pelvic floor dysfunction or dyssynergia. Either alterations in pelvic floor anatomy or function can result in impaired ability to defecate effectively. Defecation requires coordinated activity that includes generation of intrarectal pressure, and relaxation of the internal and external anal sphincters, perineal muscles, as well as the levator ani including the puborectalis muscle (272). Incorrect technique, structural abnormalities (e.g., rectocele), and pudendal and perineal nerve damage can contribute to incomplete defecation (273). Symptoms and signs include straining, incomplete evacuation, and digital maneuvers. Complications can include rectal prolapse, rectocele, and anal fissures.

Typical features of pelvic floor dyssynergia include incomplete relaxation or paradoxical contraction of the anal canal, paradoxical contraction of the puborectalis muscle, or uncoordinated movement of the abdominal, rectal, and anal muscles. As such, the goals of biofeedback are to provide a tailored approach to correction of improper defecatory technique. Trained physical therapists use a variety of techniques and tools to assess and correct underlying technical abnormalities.

Biofeedback, performed by a trained and skilled therapist, is effective in relief of constipation symptoms in CIC patients with demonstrated evidence of pelvic floor dyssynergia.
Recommendation: weak. Quality of evidence: low.

A total of nine randomized clinical trials (274–282) of patients with CIC with pelvic floor dyssynergia were identified. Six were excluded because either they did not report a relevant outcome (277) or data were not extractable (278) or they compared biofeedback with balloon-assisted training or different forms of biofeedback (279–282), leaving three randomized clinical trials (274–276) that evaluated 216 patients that compared biofeedback to a sham therapy or PEG laxative. All trials were unclear or at high risk of bias because of inability to blind participants to the nature of the interventions, or a lack of reporting of methods used to generate the randomization schedule or conceal allocation. There was a statistically significant benefit of biofeedback (RR constipation not improved = 0.33, 95% CI 0.22–0.50) with the NNT of 2 (95% CI 1.6–4) and no statistically significant heterogeneity.

None of the eligible trials (274–276) reported on adverse events.

Summary: Although techniques may vary in precise methodological details, biofeedback administered by a skilled and experienced therapist is, in general, effective in the management of patients with CIC who have prominent features of pelvic floor dyssynergia. Access to such expertise limits the usefulness of this approach for many patients and their physicians.

6. Bile acid transporter inhibitors in CIC

The ileal bile acid transporter (IBAT) inhibitor A3309 is a promising new therapy for CIC.
Grading not appropriate as no implication for current CIC management.

The IBAT is the most important transporter of the bile acid reabsorption loop. IBAT inhibitors selectively inhibit the reuptake of bile acids in the ileum, resulting in increased secretion and motor activity in the colon. Recently, the IBAT inhibitor A3309 has been proposed as a potential treatment for CIC.

We identified 3 RCTs of the bile acid transporter inhibitor A3309 in CIC involving 256 patients (283–285). All three trials were at low risk of bias. Varying doses of A3309 were employed ranging from as low as 0.1 mg to as high as 20 mg. Responses were dose dependent. In the largest study to date (283), an increase of ≥1 complete spontaneous bowel movements per week over baseline for 4 of the 8 weeks of the study was reported for 58, 64, and 75% of those randomized to 5, 10, and 15 mg of A3309, respectively, compared with 33% for placebo.

Diarrhea was more common in the patients receiving A3309 compared with placebo (RR = 2.62, 95% CI 0.72–9.56).

7. Probiotics in CIC

There is insufficient evidence to recommend probiotics in CIC. Recommendation: weak. Quality of evidence: very low.

We identified three trials evaluating probiotics in 245 CIC patients (286–288). None of the eligible trials stated the method of randomization or concealment and one was an open design. In two trials (286,288), the risk of bias was deemed to be unclear and one (287) had a high risk of bias. There were two trials (286,287) that reported on improvement in constipation in 110 CIC patients. Although both trials were positive in favor of probiotics improving constipation, the pooled data were not statistically significant (RR = 0.29, 95% CI 0.07–1.12) in a random effects model as there was significant heterogeneity between the two trials. There were two trials (287,288) that reported on mean number of bowel movements per week in 165 patients. There was a significant improvement in the mean number of bowel movements per week (mean increase in bowel movements per week in the symbiotic group = 1.49, 95% CI 1.02–1.96).

CONFLICT OF INTEREST

Guarantor of the article: Eamonn M.M. Quigley, MD, FACG.

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