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Irritable bowel syndrome: new and emerging treatments

Magnus Halland, Yuri A Saito

Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester, MN 55905, USA

Correspondence to: Y A Saito
saito.yuri@mayo.edu

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ABSTRACT

Irritable bowel syndrome is one of the most common gastrointestinal disorders in developed nations. It is characterized by abdominal pain, altered bowel habits, and bloating. Several non-pharmacological and pharmacological agents, which target the peripheral gastrointestinal system and central nervous system, are used to treat the syndrome. The individual and societal impact of investigating and managing the syndrome is substantial, and despite newer treatments, many patients have unmet needs. Intense research at many international sites has improved the understanding of pathophysiology of the syndrome, but developing treatments that are effective, safe, and that have tolerable side effects remains a challenge. This review briefly summarizes the currently available treatments for irritable bowel syndrome then focuses on newer non-pharmacological and pharmacological therapies and recent evidence for older treatments. Recent guidelines on the treatment of irritable bowel syndrome are also discussed.

Introduction

Irritable bowel syndrome (IBS) is a common gastrointestinal disorder characterized by abdominal pain or discomfort in conjunction with altered bowel habits. Bloating or abdominal distension is also common.

IBS remains a symptom based diagnosis because objective tests are currently lacking. The most recent Rome III criteria for a diagnosis of IBS stipulate recurrent abdominal pain or discomfort on at least three days a month in the past three months associated with two or more of the following: improvement with defecation, onset associated with a change in stool frequency, and onset associated with change in stool form (box).[1]

IBS can be clinically subtyped into IBS with constipation (IBS-C), defined as more than 25% stools being hard or lumpy and less than 25% of stools being loose or watery. Conversely, IBS with diarrhea (IBS-D) is defined as more than 25% of stools being loose or watery and less than 25% of stools being hard or lumpy. Patients who have more than 25% stools being hard and lumpy and more than 25% being loose and watery are diagnosed as having mixed IBS (IBS-M).

Rome III diagnostic criteria for irritable bowel syndrome (IBS) and subtypes[1]

IBS criteria

Recurrent abdominal pain or discomfort for at least three days per month in the past three 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

IBS subtyping by predominant stool pattern

- IBS with constipation (IBS-C):
  - Hard or lumpy stools ≥25% of bowel movements
  - Loose or watery stools <25% of bowel movements
- IBS with diarrhea (IBS-D):
  - Loose or watery stools ≥25% of bowel movements
  - Hardy or lumpy stools <25% of bowel movements
- Mixed IBS (IBS-M):
  - Hard or lumpy stools ≥25% of bowel movements
  - Loose or watery stools ≥25% of bowel movements
- Unsubtyped IBS:
  - Does not meet criteria for IBS-C, IBS-D, or IBS-M

Epidemiology

Global estimates of prevalence vary from 5% to 15%.[2-5] A recent meta-analysis of population based studies confirmed a modest predominance of IBS in women, which varied according to the definition of IBS (Manning or Rome I, II, or III) used. In all eligible studies (using various IBS definitions), the overall odds ratio for IBS in women versus men is 1.67 (95% confidence interval 1.53 to 1.82).[6] The pooled prevalence for women is 14.0% compared with 8.9% in men. Women are more likely than men to seek medical attention for the condition and to report IBS-C,[7] whereas IBS-D is more common in men.[6] The prevalence of IBS decreases with increasing age, and new onset of symptoms after 50 years is uncommon.[5]

IBS clearly affects patients' quality, but not quantity, of life.[8-11] The financial impact of IBS for patients, healthcare systems, and society is substantial.[12] For example, a recent review found that the average cost per patient per annum was $742 (£490; €667) to $7547 in the United States, compared with £90 to £316 in the United Kingdom and €567

to €862 in France.[12] Furthermore, a large survey of patients with IBS found that the average number of sick days taken per person per year was 30 in the US.[13] About 30% of people with IBS seek regular medical care, and in the US an estimated 12% of primary care visits and about 30-50% of gastrointestinal consultations are related to IBS.[14-16]

Pathogenesis

Established factors in the pathogenesis of IBS include diet (food intolerance and sensitivity), psychological factors (stress, coping, abuse, comorbid depression, anxiety, and somatization), alterations in gut motility, visceral hypersensitivity, differential central nervous system processing of afferent gut signals, differences in colonic microbiota, and immune responses after infection.[17-20] Twin studies and family studies confirm familial aggregation of IBS, supporting a genetic and environmental basis for the syndrome.[21-24] Although a definitive IBS gene or set of genes has yet to be identified,[25] several promising leads suggest that abnormalities in serotonin receptors, sodium ion channels,[26] proteins involved in the immune response,[27] or proteins in bile acid metabolism[28] may play a role in a subset of people with IBS. IBS therefore seems to be a complex heterogeneous disorder that results from the interplay of environmental and genetic factors.

The above risk factors are not found uniformly in all patients, making the mechanisms of IBS more difficult to understand. For example, only 25-75% of patients with IBS have altered gut motility.[29 30] It is likely that multiple factors are at play in most patients, so a single treatment modality is unlikely to provide a cure for all patients. Nonetheless, an understanding of the potential contributors may help providers and patients to select the best therapeutic approach.

Clinical approach

Because the symptoms of IBS are non-specific, in clinical practice tests may be needed to rule out other diseases before a conclusive diagnosis of IBS is made. However, progress towards developing a reliable biomarker assay is being made.[31-33]

Because IBS symptoms are often diverse, a multifactorial treatment approach is usually needed. This includes reassurance and education by the provider, and diet and lifestyle modification by the patient. Although many patients have mild symptoms and have adequate relief with simple measures, others may not.[34] The intrusive nature and severity of symptoms can lead to severe functional impairment such as limitations at work and school, at home, and in social situations, as well as difficulty leaving home.[34] The need for improved treatments is shared by patients and providers alike.

Although several therapies are available to treat IBS symptoms, this review focuses on new developments or evidence in the management of IBS, including non-pharmacological and pharmacological approaches.

Overview of conventional treatments

Non-pharmacological

Several non-pharmacological therapies exist for IBS, including structured patient education,[35 36] dietary manipulation,[37] and stress management_ENREF_1.[38-40] Patient education can be geared towards explaining IBS as a diagnosis, reassurance that the symptoms do not suggest a more serious underlying illness, and counseling on lifestyle factors that may attenuate symptoms. Dietary management may include general counseling about foods that can exacerbate symptoms (such as excess caffeine, carbonated drinks, and gas producing foods). Stress management may include acknowledging the presence of life stressors and discussing coping mechanisms. However, a referral to a psychologist or behavioral therapist for evaluation and treatment for stress, anxiety, or depression may be warranted.

Pharmacological

Pharmacological approaches often target one or more pathophysiological abnormality that is involved in the pathogenesis of IBS and are aimed at the dominant symptom. Several management options are available including some without prescription and others that need a prescription. Over the counter treatments include fiber supplements, simeticone, lactase enzyme tablets, digestive aids (such as α-galactosidase) and supplements, anti-diarrheal agents, probiotics, and numerous osmotic and stimulant laxatives. Pharmacological treatments requiring a provider prescription include antispasmodics, antidepressants, specific laxatives, and other agents that hasten or slow down intestinal motility.

The risks and benefits of treatment need to be assessed on an individual basis. Below, we provide an update on new as well as emerging pharmacological and non-pharmacological therapies.

New non-pharmacological treatments

This section focuses on newer IBS treatments, many of which have been introduced in the past three to five years. It also provides information on older treatments for which more recent data on safety or efficacy are available.

Sources and selection criteria for new treatments

We searched Medline and Embase using the terms “irritable bowel syndrome” and “therapy” from the inception of these databases until November 2014. We also used our reference lists and personal libraries to identify supplemental information. The full text of articles published in English, Norwegian, Swedish, and Danish was reviewed, and English abstracts were reviewed for all other languages. We prioritized evidence obtained from systematic literature reviews, meta-analyses, and randomized controlled trials (RCTs) published during the past five years when available.

Dietary therapies

Patients often report dietary triggers for their symptoms, although no specific food item has been conclusively implicated in the pathogenesis of IBS.[41 42] The potential mechanisms for this food intolerance include osmotically active chemicals (for example, sorbitol), carbohydrate intolerance (for example, lactose), stimulation of gastrointestinal transit (for example, caffeine), food allergies, enhanced gastrocolic reflex, and colonic fermentation.[43]

Food category	Low FODMAP examples	High FODMAP examples
Dairy products 	• Lactose-free dairy products • Hard cheeses	• Ice cream • Milk (including goats' milk) • Soft cheeses (camembert/brie) • Yoghurt • Cream
Vegetables 	• Bean sprouts, bok choy • Capsicum, carrots, celery, cucumber, corn • Eggplant, lettuce, leafy greens • Pumpkin, potatoes • Tomatoes, zucchini, all fresh herbs	• Artichokes, asparagus • Beetroot, broccoli, brussel sprouts • Cabbage, cauliflower, fennel, green beans, garlic • Mushrooms, okra, onions • Snow peas, squash
Fruits 	• Bananas, berries, cantaloupe melon • Grapes, grapefruit, honeydew melon, kiwi • Lime, passion fruit, pineapple • Rhubarb, all citrus fruits	• Avocado, apples, apricots • Cherries, dates, dried fruits, figs • Mango, nectarines • Papaya, peaches, pears, plums, prunes • Watermelon
Meats and protein sources 	• Fish, meat, chicken, tofu, shellfish, eggs	• Legumes, pulses
Breads and cereal 	• Spelt and gluten-free bread • Rice cereal, rice quinoa, gluten-free pasta	• Wheat and wheat based bread • Cereals, rye, wheat, pasta
Food additives, spices, and condiments 	• Most spices and herbs • Mayonnaise • Olives, onion powder, olive oil, pepper, salt • Maple syrup without high fructose corn syrup, mustard • Soy sauce, chili sauce • Sugar • Vinegar (including balsamic vinegar)	• Any food with high fructose corn syrup or agave syrup content • Artificial sweeteners including sorbitol, mannitol, isomalt, xylitol (cough drops, gums, mints) • Chutneys, coconut, honey, jams, jellies • Molasses, pickles, relishes

Low and high FODMAP (fermentable oligosaccharides, disaccharides, monosaccharides, and polyols) containing food

Studies of exclusion diets, including dairy and wheat, have yielded conflicting results. For example, one RCT reported a 10% reduction in symptoms when IgG based testing was used to guide dietary recommendations compared with a sham diet.[44] However, an older study found that a diet challenge with food that led to positive IgG titres and skin test results in patients with IBS did not exacerbate symptoms.[45] Food allergy testing for IBS is therefore highly controversial and is not advocated by most academic experts and clinicians.

A systematic review of 30 trials of dietary intervention conducted by the British Dietetic Association graded the evidence for specific interventions:

- Grade A: based directly on level I evidence
- Grade B: based directly on level II evidence or extrapolated recommendations from level I evidence
- Grade C: based directly on level III evidence or extrapolated from level I or II evidence
- Grade D: based directly on level IV evidence or extrapolated from level I-III evidence.[46]

The evidence for each clinical practice recommendation was summarized as follows:

- A low lactose diet if lactose sensitivity is suspected and testing is not available or if there is a positive lactose breath test (grade D)
- A milk-free diet (or alternatively, mammalian milk) if milk is thought to be a trigger in spite of a low lactose diet (grade D)
- Avoid dietary supplementation with wheat bran (grade C)
- A three month trial of ground linseeds for patients with IBS-C (grade D)
- Assess intake and consider reduction in intake of fermentable carbohydrates (grades B and D)
- Probiotics can be considered and are not thought to be harmful (grade B)
- Consider an elimination or empirical diet for two to four weeks if food is an IBS trigger (grade D).

These guidelines were constructed for dietitians in practice. Much of the evidence was of poor quality and future research is needed to answer many clinical questions.

Fermentable carbohydrates

Several recent retrospective and prospective studies have suggested that a diet low in fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAPs) is beneficial.[47-51] Foods high in these poorly digested carbohydrates are thought to cause IBS symptoms through their osmotic effects and fermentation by colonic bacteria, which leads to gas production, as well as their direct effects on gastrointestinal motility.[42] The figure provides a list of low and high FODMAP foods.

Supportive evidence for the efficacy of a low FODMAP diet is limited. The first randomized trial in IBS studied 41 people (with six dropouts) over four weeks. In the intention to treat analysis, those on the low FODMAP diet were significantly more likely to report adequate control of global IBS symptoms compared with those receiving the standard diet (68% *v* 23%; P=0.005).[48] Self rated symptoms of pain, bloating, and flatulence improved the most, with no difference between the two dietary arms for symptoms of diarrhea or constipation.

In a recent double blind, randomized, controlled crossover trial, 30 people with IBS and eight healthy controls were given a standard diet versus a low FODMAP diet for three weeks.[37] The standard and low FODMAP diets were delivered to the participants' homes and 83% of the participants completed the study. The participants were given lists of extra foods that were allowed for each study period. The primary outcome was defined as a change in overall gastrointestinal symptoms on a 100 mm visual analog scale. People with IBS had significantly (P<0.001) lower scores 22.8 (16.7 to 28.8) while eating the low FODMAP diet compared with the standard diet 44.9 mm (36.6 to 53.1). People with all subtypes of IBS reported significantly greater satisfaction with stool consistency as assessed by a visual analog scale while on the low FODMAP diet, although altered fecal frequency and stool consistency, as assessed by the King stool chart rating,[52] scores were recorded only in those with IBS-D.

Although these two prospective, randomized trials report positive findings, several weaknesses and criticisms

remain about the literature to date, including a limited number of trials, small sample sizes, insufficient blinding to received diet, use of unvalidated endpoints, borderline findings, and lack of long term data on sustainability and benefit.[53] Because patients often request dietary guidance from their providers, a low FODMAP diet could be cautiously considered for patients with IBS symptoms who have dietary sensitivity, particularly those with bloating, gas, or excess flatulence.

Gluten

Gluten is a protein found in wheat, rye, and barley that lends an elastic property to foods such as breads and doughs. With increasing public awareness of gluten and gluten-containing foods, many patients with IBS now avoid gluten or try a gluten-free diet. The concept of immune-mediated non-celiac gluten sensitivity has been proposed.[18] One observational study suggested that gluten withdrawal leads to improvement in symptoms among some patients with IBS-D, particularly those who carry celiac permissive genes (HLA-DQ2 and HLA-DQ8).[54] Two RCTs conducted in patients with IBS in whom celiac disease had been excluded showed that those randomized to a gluten containing diet were more likely to experience symptoms than those allocated to a gluten-free diet.[55 56] This has recently been challenged by another double blind, placebo controlled, crossover trial, in which 37 people with self-reported gluten sensitivity were initially placed on a low FODMAP diet.[57] They were subsequently randomized to a high gluten (16 g gluten/day), low gluten (2 g gluten/day plus 14 g whey/day), or control (16 g whey/day) diet, and no evidence of a dose dependent effect was seen. Currently, the independent effect of gluten protein, excluding its role as a FODMAP containing food, is not clear.

Fiber

Dietary fiber comprises non-digested plant material that is insoluble (for example, whole grains and wheat) or soluble (for example, oats, psyllium, and flax) in water. Fiber has been recommended for years to treat IBS and constipation, although fiber related gas production can exacerbate bloating and flatulence in patients with IBS. A recent meta-analysis of 14 RCTs with 906 patients found a significant benefit of soluble fiber in global IBS symptoms (relative risk 0.83, 0.73 to 0.94), with a number needed to treat of 10, whereas bran, although not harmful, was not effective (0.90, 0.79 to 1.03).[58]

Exercise

Physical activity improves quality of life in several medical conditions, including fibromyalgia, depression, and colon cancer.[59-61] Because exercise improves gas transit and defecatory patterns, a potential benefit in IBS is plausible.[62] Furthermore, regular exercise may reduce stress and affect visceral hyperalgesia through central pathways.[19]

A single RCT of 102 patients with IBS allocated patients to regular phone support that encouraged 20-60 minutes of physical activity three to five times a week versus phone support that encouraged maintenance of current lifestyle. The main finding was that patients randomized to exercise had a significantly greater improvement in symptoms compared with the control group as assessed by the IBS symptom severity score (exercise group −51 (−130 and 49) *v* controls −5 (−101 and 118); P=0.003).[63] Patients randomized to exercise also had less worsening of symptoms than physically inactive patients. No other randomized trials have been performed to validate these findings, but given the multiple benefits of physical activity, a trial of increased physical activity for people with low activity levels could be recommended.

Biofeedback therapy for IBS-C

Many patients with IBS-C, and some without constipation, describe difficulty with evacuation.[64] Incomplete evacuation due to dys-synergic defection may contribute to IBS symptoms by retention of stool and gas.[65] The diagnosis is often suspected from the symptoms (for example, straining, passage of thin stools, incomplete evacuation, and less commonly facilitation of stool passage by anal digitation or manual support of perineal structures during defecation) and an abnormal dynamic digital rectal examination during simulated defecation. The diagnosis can be confirmed by anorectal manometry.[66-68]

Biofeedback refers to pelvic floor retraining, typically administered by trained physiotherapists, which emphasizes correction of abnormalities such as paradoxical contraction of the anal canal or other pelvic floor muscles with defecation. One prospective observational study assessed the impact of biofeedback therapy in 50 patients with and without IBS who had confirmed dys-synergic defecation.[69] Patients, 29 of whom fulfilled Rome II criteria for IBS-C, had weekly biofeedback sessions that lasted 45-60 minutes and consisted of visual and verbal feedback guided by a solid state anorectal manometry catheter for four weeks. Biofeedback therapy was successful (as defined by a 50% improvement in constipation based on a visual analog scale) in 30 patients, of whom 22 fulfilled criteria for IBS-C at the start of the study. Sixteen of these patients no longer fulfilled criteria for IBS-C after biofeedback therapy, and the resolution of IBS symptoms correlated with improved defecation indices. The success of this treatment was not affected by IBS status, highlighting the need to screen patients with IBS-C for dys-synergic defecation and consider biofeedback therapy in motivated patients if such treatment is locally available.

Probiotics

Probiotics are live bacteria that are thought to confer a health benefit in the host. Given that an abnormal microbiome may be implicated in the pathogenesis of IBS,[70-72] it has been proposed that manipulation of the microflora by probiotics may be therapeutic. Several probiotic products are currently available, and different brands contain different organisms, single or multiple organisms, and varying quantities of organisms. The most common bacteria found in probiotics are species of *Lactobacillus* and *Bifidobacterium*.

Six systematic reviews with meta-analyses have attempted to summarize the findings of multiple randomized trials.[73-78] The general consensus is that probiotics show modest

benefit, with an estimated number needed to treat of 4. However, the heterogeneous patient groups, including mixture of the patients with differing IBS subtypes, the variety of probiotic formulations used, and different outcomes measured make the results difficult to interpret.

A systematic review published in 2013 assessed probiotics in patients with various lower gastrointestinal conditions, including IBS, and generated guideline statements on the clinical applications of probiotics.[78] Evidence for each symptom or clinical problem was graded by consensus of a panel of 10 experts. The review identified 37 randomized placebo controlled trials in adults, 19 of which focused on IBS. The panel concluded that "specific" probiotics can help overall IBS symptoms; overall IBS symptoms in some patients with IBS-C and IBS-D; and specific symptoms such as abdominal pain, bloating, constipation, and frequency or consistency of bowel movements. The panel found no benefit for probiotics in reducing flatus or diarrhea.

A systematic review and meta-analysis published in 2014 evaluated RCTs in adults with IBS, as well as chronic idiopathic constipation.[76] It found that probiotics reduced IBS symptoms compared with placebo (relative risk 0.79, 0.70 to 0.89). Probiotics had a positive impact on global IBS symptoms as well as abdominal pain, bloating, and flatulence. On the basis of this review and others, probiotics as a class seem to confer symptomatic benefit, but the ideal patient who would benefit, optimal probiotic formulation (organisms and dose), and duration of treatment have yet to be identified. Furthermore, suboptimal study design has been highlighted as a problem,[74] and as such, the real estimate of probiotic efficacy remains to be determined.

Herbal therapies

Many patients with IBS take or express an interest in taking herbal therapies.[79] A systematic review performed in 2006 identified 75 RCTs of herbal therapy in IBS, although only three were deemed to be of high quality.[80] Seventy one different herbal formulations were assessed in trials that compared herbal medicines with placebo or conventional treatment. Peppermint oil has also been shown to be superior to placebo in controlled trials. Thus, overall the following herbal preparations have shown a significant improvement of global symptoms compared with placebo in high quality trials:

- A standard or individualized Chinese herbal formula[81]
- STW 5 (Iberogast)[82]
- Tibetan herbal medicine Padma Lax[83]
- Peppermint oil.

Standard or individualized Chinese herbal formula

A randomized, double blind trial of 116 patients with IBS compared the effect of a standard Chinese herbal formula consisting of 20 dried, powdered, and encapsulated herbs with that of an individualized formula designed by a Chinese medical herbalist. After 16 weeks, patients who received the standard formula, the individualized formula, or placebo reported a 44%, 42%, and 22% reduction in symptoms (as measured with a validated bowel score), respectively (P=0.03 across all groups). Thus, in this trial, both a standard and individualized Chinese herbal formula seemed to be effective.

STW 5 (Iberogast)

STW 5, a liquid multi-drug herbal supplement, has been studied in clinical trials of gastrointestinal conditions such as IBS and functional dyspepsia. Components include bitter candytuft, angelica root, chamomile flowers, caraway fruit, St Mary's thistle, lemon balm leaves, peppermint leaves, celandine, and liquorice root. This herbal preparation is available over the counter in many countries, or from online vendors without a prescription. In vitro, STW 5 has been shown to affect gastrointestinal transit, gastric accommodation (reduced gastric tone and increased compliance after a meal), and small intestinal secretion, thereby providing a plausible physiological mechanism to explain the clinical benefits seen in trials.[84-86] For example, when human cells were exposed to STW 5, there was a dose dependent increase in ion secretion that was significantly reduced by the Na-K-Cl cotransporter blocker, bumetanide, indicating a secretagogue effect.[84] Also, in experiments using a rat model, components of STW 5 have been shown to bind both muscarinic (M3) and serotonergic receptors (5-HT_4 and 5-HT_3), both of which affect gastrointestinal motility and sensation.[85]

A review published in 2013 assessed data on the safety and efficacy of STW 5 in functional gut disorders including IBS.[87] Of the 12 studies in the review, two specifically looked at IBS, but only one was randomized and placebo controlled.[82] The study comprised 208 patients and the main outcomes were abdominal pain and IBS scores. An intention to treat analysis showed that STW 5 was significantly superior to placebo at reducing the abdominal pain score (P=0.0009) and the global irritable bowel symptom score (P=0.001) at four weeks. Safety data from 12 prospective and retrospective studies of STW 5 showed that 0.04% of patients reported adverse effects, none serious.[87] Preclinical testing and post-marketing review over five decades has also failed to show any acute or chronic toxicity, with no safety signals relevant for human use observed.[87]

Peppermint oil

Peppermint oil has been used for centuries for various gastrointestinal ailments. A systematic review published in 2014 identified nine relevant studies that looked at 726 patients.[88] Peppermint oil was significantly superior to placebo for global improvement of IBS symptoms (five studies, 392 patients; relative risk 2.23, 1.78 to 2.81) and improvement in abdominal pain (five studies, 357 patients; 2.14, 1.64 to 2.79). Patients taking peppermint oil were significantly more likely to experience an adverse event, but such events were mild and transient in nature—22% of those taking peppermint oil experienced at least one adverse event versus 13% of those taking placebo (relative risk 1.73, 1.27 to 2.36). The most commonly reported adverse event was heartburn.

Therefore, at the time of writing, STW 5 and peppermint oil are the only readily available herbal treatments that have convincing data from randomized trials to recommend their routine clinical use.

CNS based therapy

Treatments for IBS such as hypnotherapy or cognitive behavioral therapy, which focus on the central nervous system (CNS), have for decades shown robust results and reproducibility across numerous studies from several different centers.[89-92] The number needed to treat has been estimated at 2-4.[89-92] However, the efficacy of these psychological interventions outside the context of a structured clinical trial is not known.

A 2014 systematic review summarized 32 RCTs of which 28 compared psychological therapies with a control therapy and four compared two specific psychological therapies in IBS[93]:

- Six trials of cognitive behavioral therapy
- Five trials of relaxation training
- Five trials of hypnotherapy
- Four trials of multicomponent psychological therapy
- Two trials of self administered or minimal contact cognitive behavioral therapy
- Two trials of internet delivered cognitive behavioral therapy
- Two trials of dynamic psychotherapy
- One trial of mindfulness medication
- One trial of stress management
- Four trials in which two different psychological therapies were compared:
  - Stress management versus cognitive behavioral therapy
  - Cognitive behavioral therapy versus self administered cognitive behavioral therapy
  - Multicomponent psychological therapy given face to face versus over the telephone
  - Cognitive behavioral therapy versus relaxation therapy.

Overall, the relative risk of symptoms not improving with psychological therapies versus a control therapy was 0.68 (0.561 to 0.76). Cognitive behavioral therapy, hypnotherapy, multicomponent psychological therapy, and dynamic psychotherapy were all beneficial.

Thus, CNS based therapies should be considered a treatment option for IBS and further explored. Unfortunately, lack of widespread access to these treatment modalities remains a challenge.

New pharmacological treatments

Antibiotics

There is a growing and controversial literature on the use of antibiotics in non-constipated IBS, particularly IBS-D. It has been suggested that antibiotics are useful in IBS alone,[20 72] and in IBS related small intestinal bacterial overgrowth.[94] Risk factors for small intestinal bacterial overgrowth include conditions associated with achlorhydria (for example, gastrectomy, advancing age, use of proton pump inhibitors), intestinal dysmotility (for example, scleroderma), anatomic alterations (for example, blind loop), and other gastrointestinal conditions, including Crohn's disease and celiac disease.[95 96] Small intestinal bacterial overgrowth has been found in 4-80% of patients with IBS.[97 98] This variation may be due to heterogeneous patient populations, use of different diagnostic tests (glucose or lactulose hydrogen breath testing (with or without methane measurement) versus quantitative culture of duodenal or jejunal aspirates), and different definitions or thresholds for normal and abnormal results.[94 97 98]

In the absence of small intestinal bacterial overgrowth, antibiotics might benefit patients with IBS by altering gut flora, which may be inherently different from the flora of people without IBS, or by simply reducing the overall number of colonic bacteria, thereby reducing the amount of intestinal gas.[99-101] Neomycin and metronidazole have been studied in single RCTs in patients with IBS and have shown varying efficacy.[102 103] Neomycin was studied in 111 patients with IBS for 10 days, and the intention to treat analysis showed a 35% reduction in composite score in the treatment group versus an 11.4% reduction in the placebo group (P<0.05). No adverse events attributed to neomycin were reported. The metronidazole study was conducted in India in 45 patients with IBS, and the mean symptom score decreased from 24.0 to 10.9 in the metronidazole arm versus 24.6 to 18.1 in the placebo arm. Several studies have shown that rifaximin improves global IBS symptom scores and symptoms such as bloating.[104-107] In the largest two studies, TARGET 1 and TARGET 2, 1258 patients with IBS without constipation were treated with 550 mg of rifaximin or placebo three times daily for two weeks and then followed for 10 weeks.[107] The primary endpoint was proportion of patients with adequate relief of global IBS symptoms for at least two of the first four weeks after treatment; the key secondary endpoint was adequate relief of IBS related bloating. In the individual TARGET studies and the combined analyses, patients taking rifaximin fared better than those taking placebo with regard to global IBS symptoms (combined: 41% *v* 32%; odds ratio 1.53; P<0.001) and IBS related bloating (combined: 40% *v* 30%; 1.56; P<0.001). In addition, patients taking rifaximin reported significantly better outcomes for other secondary endpoints, including daily abdominal pain and daily stool consistency (P <0.001). A 2012 systematic review of five RCTs found that rifaximin was associated with a greater odds of global IBS symptom improvement than placebo (odds ratio 1.57, 1.22 to 2.01), with a number needed to treat of 10.[107] This review also found comparable rates of adverse events for rifaximin and placebo. Because of high placebo response rates, the beneficial effects of rifaximin seem to be clinically modest, although statistically significant. The duration of follow-up was also relatively short (10-12 weeks).

Pharmacotherapy for IBS-D: serotonin receptor antagonists

Because more than 95% of the body's serotonin is located in the gastrointestinal tract and 5-HT_3 and 5-HT_4 receptor manipulation has been shown to alter gastrointestinal transit (for example, with alosetron and tegaserod),[108-110] serotonin is a viable therapeutic target. A randomized crossover trial published in 2013 assessed whether ondansetron, a $5HT_3$ receptor antagonist traditionally used for nausea and vomiting, would be useful because of its constipating effect.[111] The trial investigated 120 patients who met Rome III criteria for IBS-D. The main

outcome was patient reported stool form, but data were also collected on other intrusive symptoms such as urgency, pain perception, and frequency of defecation. Ondansetron significantly improved stool consistency (mean difference in stool form as recorded by the Bristol stool form score) between ondansetron and placebo was −0.9, −1.1 to −0.6; P<0.001). Compared with placebo, patients on ondansetron had fewer days with urgency (P<0.001), lower urgency scores (P<0.001), reduced frequency of defecation (P=0.002), and less bloating (P=0.002). No significant change in pain scores was observed. The IBS symptom severity score decreased more in patients taking ondansetron than in those taking placebo (83 (standard deviation 9.8) *v* 37 (9.7); P=0.001). In addition, 65% reported adequate relief (as assessed by the question "over the last two weeks did you obtain adequate relief of your IBS symptoms?") with ondansetron but not placebo compared with 14% reporting relief with placebo but not ondansetron (relative risk 4.7, 2.6 to 8.5; P<0.001). However, the dropout rate in people taking ondansetron was 23%, and those with the most severe diarrhea were more likely to drop out.

Pharmacotherapy for IBS-C

Chloride channel activators

Newer prescription drugs for IBS-C include laxatives such as lubiprostone. This type 2 chloride channel activator of intestinal apical epithelial channels causes an influx of chloride and fluid into the intestinal lumen. This action results in altered stool consistency and enhanced intestinal transit, thus yielding greater spontaneous bowel movements.

Lubiprostone does not seem to work through altering colonic motor or sensory function,[112] and it has also been approved for use in chronic constipation and opioid induced constipation. To date, four clinical trials of the use of lubiprostone in IBS have been published. A phase II dose finding study found that lubiprostone at three doses (8 µg, 16 µg, and 24 µg twice daily) significantly improved mean abdominal discomfort and pain scores compared with placebo at one month (P=0.023). After two months, all patients taking lubiprostone showed significantly greater improvements in mean abdominal discomfort and pain scores (P=0.039).[113] A combined analysis of two phase III trials of 1171 patients with IBS-C taking lubiprostone 8 µg twice daily versus placebo found that significantly more patients taking lubiprostone had greater IBS symptom relief. The analysis assessed symptom relief by responses in the weekly electronic diary to the question "How would you rate your relief of IBS symptoms over the past week compared to how you felt before you entered the study?"(17.9% *v* 10.1%; P=0.001).[114] In a subsequent trial of 170 patients with constipation, of whom 42 also had IBS, lubiprostone at a dose of 48 µg a day significantly increased spontaneous bowel movements per week.[115]

These studies consistently suggest a positive clinical effect of lubiprostone on constipation symptoms. Prescription dosing for IBS is 8 µg twice daily, although 24 µg twice daily is available for chronic idiopathic constipation and opioid induced constipation.

Guanylate cyclase C agonists

Linaclotide is a 14 amino acid peptide agonist of guanylate cyclase 2C. The guanylate cyclase 2C transmembrane receptor is expressed in the human intestine and is typically activated by guanylin or uroguanylin. This laxative has also been approved for use in chronic idiopathic constipation.

Three large randomized, double blind, multicenter, placebo controlled studies have assessed linaclotide. The first was a phase IIb dose finding study that investigated 75 µg, 150 µg, 300 µg, and 600 µg of linaclotide daily versus placebo for 12 weeks in 420 patients with IBS-C.[116] Abdominal pain was significantly reduced from baseline in people taking linaclotide compared with those taking placebo. Mean changes in abdominal pain (assessed on a 5 point scale) from baseline were −0.71, −0.71, −0.90, and −0.86 for linaclotide doses of 75 µg, 150 µg, 300 µg, and 600 µg, respectively, compared with −0.49 for placebo (P=0.03).

The second study was a 26 week phase III trial of 804 patients that compared 290 µg of linaclotide once daily with placebo.[117] Using the Food and Drug Administration definition of response (>30% reduction in abdominal pain and increase of at least one complete spontaneous bowel movement per week for 50% of the treatment period), 34% of those on linaclotide responded compared to 14% of those on placebo (odds ratio 3.2, 2.2 to 4.5; P<0.0001). Improvements were significantly greater in the linaclotide arm for abdominal pain, number of spontaneous bowel movements, bloating, stool form, and straining.

The third study was a phase III trial of 800 patients that compared 290 µg of linaclotide daily with placebo for 12 weeks.[118] The study included a 12 week treatment period as well as a four week randomized withdrawal period. For at least six of the 12 treatment weeks, significantly more patients taking linaclotide reported a 30% reduction in abdominal pain (50.1% *v* 37.5%; P=0.0003) and an increase of at least one complete spontaneous bowel movement from baseline (48.6% *v* 29.6%; P<0.0001). Furthermore, during the randomized withdrawal period, patients who remained on linaclotide maintained their improvement, whereas those randomized to change from linaclotide to placebo showed a return of symptoms. These studies consistently show that linaclotide reduces symptoms, but the most recent study shows that long term treatment may be needed for those with chronic symptoms.[118] Approved prescription dosing of linaclotide is 290 µg orally once daily for IBS, although a lower dose 145 µg tablet is also available for chronic idiopathic constipation.

Emerging treatments

Herbal therapies

A recent trial compared the Korean herbal medicine Gwakhyangjeonggisan, with or without a probiotic supplement, with placebo in 64 patients with IBS-D.[119] The primary outcome was adequate relief from abdominal pain and discomfort. No significant difference was found between Gwakhyangjeonggisan, with or without probiotic, and placebo, although there were more responders

in the non-placebo arms. Further studies are needed to define whether this herbal therapy, with or without a probiotic supplement, has a role in the treatment of IBS.

CNS therapies

The uptake of psychological therapies for IBS has been low, perhaps because of the perceived stigma related to mental health diagnoses and therapies, the time intensive nature of treatment, limited access to experienced providers, and related costs. The experience of individual therapists, patients' adherence to treatment, and the number of sessions needed may also vary considerably. Therefore, the efficacy of less resource intensive regimens, which require less face to face contact, as well as internet based therapies is relevant. Psychological treatments that require minimal contact usually place great emphasis on the self management of symptoms. Contact with healthcare professionals is generally limited to a small number of face to face sessions (or possibly, none at all), supplemented or replaced by computer assisted therapy, telephone support, or online support (or a combination thereof).[120]

A 2014 systematic review found no significant benefit for self administered or minimal contact cognitive behavioral therapy and internet delivered therapies compared with control therapy (relative risk 0.53 (0.17 to 1.66) and 0.75 (0.48 to 117), respectively). However, further studies are needed because of the low number of high quality trials with considerable heterogeneity.[93]

Opioid agonists and antagonists

Asimadoline, a κ-opioid agonist, may have peripheral analgesic effects and hence be effective for abdominal pain associated with IBS.[121] Results of phase IIB trials in patients with high baseline abdominal pain scores were promising and the safety profile excellent.[122] However, the role of asimadoline in the management of IBS is unclear and no trials in patients with IBS are currently under way.

Furthermore, eluxadoline, a mixed μ-opioid receptor agonist and δ-opioid receptor antagonist was found to be superior to placebo in a phase II study of patients with IBS-D. Significantly more patients receiving 25 mg (12.0%) or 200 mg (13.8%) eluxadoline met the primary endpoint of clinical response than patients given placebo (5.7%; P<0.05). Patients receiving eluxadoline at 100 mg and 200 mg also had greater improvements in bowel movement frequency and urgency, global symptoms, quality of life, and adequate relief assessments (P<0.05).[123] Results from phase III trials are awaited.

Serotonin receptor antagonists

Ramosetron, another 5-HT_3 receptor antagonist, has similar pharmacologic properties to alosetron. A randomized trial published in 2014 that looked at 296 men with IBS found that 5 μg of ramosetron improved stool consistency compared with placebo (50.3% *v* 19.6%; P=0.001) and improved overall IBS symptoms and quality of life.[124] Currently, more information about the potential for ischemic colitis and reproducibility of efficacy and safety in a non-Japanese and female population is awaited.

5-HT_4 receptor agonists

Prucalopride is a highly selective 5-HT_4 receptor agonist that stimulates gut motility in vitro and in vivo and is approved for the treatment of chronic constipation in women in Europe,[125] although IBS is not an approved indication for this drug. Systematic reviews of patients with chronic constipation show a positive effect on colonic transit time and patient outcomes such as bowel frequency and quality of life.[126 127]

Guanylate cyclase C agonists

Plecanatide, an experimental 16 amino acid guanylate cyclase C agonist, is another potential emerging treatment for IBS-C, and is currently undergoing clinical trials (NCT01722318). An earlier phase I trial in 72 healthy volunteers demonstrated safety and tolerability.[128]

Mast cell stabilizers

Because of the putative role of mast cells in the pathophysiology of IBS, disodium cromoglycate, a mast cell stabilizer, is being evaluated in an animal model of IBS and was recently found to significantly decrease abdominal pain behaviors induced by colorectal distension compared with a saline control (P<0.05).[129] Furthermore, this molecule also inhibited mast cell stimulated colonic ion transport, an effect seen only in stress sensitive rats. A randomized trial of ketotifen seemed to increase the sensory threshold for discomfort during a rectal barostat in patients with IBS and visceral hypersensitivity. However, after eight weeks of treatment no significant difference was seen in relief of symptoms (20% *v* 10%).[130]

Luminal adsorbents

AST-120, a carbon based adsorbent has been evaluated in a double-blind randomized trial of 115 patients with IBS-D.[131] The exact mechanism of action is unclear, but the drug probably binds substances that are raised in the gut lumen of patient with IBS, such as histamine, serotonin, bacterial products, and bile acids. AST-120 seemed to be safe and well tolerated and improved symptoms; 32% of recipients reported a 50% or greater reduction in days with abdominal pain compared with 25% in the placebo group. These modest results were statistically significant at four weeks but the results have not been validated in long term studies.

Bile acid binders

Recent developments in the understanding of the pathophysiology of IBS and emerging diagnostic tests may change the way these drugs are used. Several recent studies have explored the impact of increased colonic exposure to bile in patients with IBS-D.[132-134] One study compared patients with IBS-D with healthy volunteers and found that colonic transit and fecal bile acid testing are useful biomarkers to identify targets for treatment in patients with IBS, with a sensitivity of 60% and specificity of 90%.[135] Furthermore, the effect of bile acid sequestrants on fecal excretion of bile acids, hepatic bile acid synthesis, and diarrhea in patients with IBS-D was recently assessed. There was a significant inverse correlation between the number of bowel movements per week

Table 1 | Selected new treatments for IBS*

Treatment	Dosing and administration	Comments on effect	NNT
Exercise[63]	20-60 minutes of moderate to vigorous physical activity 3-5 days/week	IBS-SSS score dropped by >50 points in 43% of patients randomized to exercise versus 26% in control arm	6
Biofeedback for IBS-C[69]	Refer to specialist center; 2-3 sessions of 45-60 minutes	Overall biofeedback therapy led to symptom relief in 12 of the 29 patients with IBS symptoms before treatment	Unknown
Probiotics	Wide variety of strains and formulations available (see Hungin et al for selection based on main symptom)[78]	Magnitude of benefit and the most effective species and doses remain uncertain	4
Iberogast (STW-5)[87]	20 drops in half a glass of water 3 times daily; available without prescription in many European countries and Australia; online vendors good option for US patients	In observational studies abdominal scores decreased by 65-80%; about 80% of physicians and patients assessed the effectiveness of STW-5 as very good or good; superiority over placebo confirmed in an RCT	5
Hypnotherapy/CBT	Refer to specialist providers; many different programs exist; recommend exploring local options as 6-12 sessions usually needed	Several RCTs in different settings and populations support long term efficacy	2-4
Rifaximin[107]	400-550 mg three times daily for 10-14 days (prescription only)	A meta-analysis found rifaximin to be more efficacious than placebo for global IBS symptom improvement; therapeutic gain over placebo = 9.8%	7-11
Lubiprostone[114]	8 µg twice daily (prescription only)	IBS-C patients on lubiprostone endorsed greater symptom relief (17.9% *v* 10.1%)	12
Linaclotide[117]	290 µg daily (prescription only)	34% of patients on linaclotide responded versus 14% of patients randomized to placebo	5

CBT=cognitive behavioral therapy; IBS=irritable bowel syndrome; IBS-C=constipation predominant IBS; IBS-SSS=irritable bowel syndrome severity scoring system; NNT=number needed to treat; RCT=randomized controlled trial.

and the total bile acid sequestered into stool during the last 48 hours of treatment.[133] Clinical tests for 48 hour stool bile acid content are emerging, so the current practice of empiric trials of bile acid binders may change into targeted treatment in patients with a defined pathophysiological mechanism.

Fecal transplantation

Because of the hypothesis that dysfunctional or abnormal gut microbiota may contribute to the symptoms of IBS and because of its relative success in treating refractory *Clostridium difficile* colitis, some studies have evaluated fecal transplants in patients with IBS. A limited number of non-randomized trials of fecal microbiota transplantation in patients with IBS have reported encouraging short term and long term results,[136 137] but these clinical observations have not been validated in well designed randomized trials to establish safety and efficacy.

Sacral nerve stimulation

Abnormal nerve signaling from the gut has been implicated in the pathogenesis of IBS, and sacral nerve stimulators have been hypothesized to be of benefit. A randomized trial assessed 21 patients with IBS-D or IBS-M who had responded to percutaneous nerve evaluation by at least a 30% reduction in their IBS symptom score.[138] Participants subsequently had a sacral nerve stimulator inserted and were randomized to one month "on" or "off" in a crossover design. A significant reduction in the Gastrointestinal Syndrome Rating Scale-IBS was seen during the month that the stimulator was turned on, and at one-year follow-up, the median IBS specific symptom score was 25 (range 13-65) compared with 62 at baseline (range 45-80; P=0.0001). Thus, in a select group of patients sacral nerve stimulation may prove to be a useful treatment.

Summary of emerging treatments

In summary, several new and emerging therapeutic options are available to complement the established treatments. The newer non-pharmacologic therapies include an emphasis on maintaining healthy routines including incorporating regular exercise, specific dietary modification, probiotic therapy, biofeedback for those with defecation disorders, and CNS based treatments. Newer pharmacologic interventions include use of non-absorbable antibiotics and targeted gastrointestinal receptor based drugs, including guanylate cyclase C agonists and serotonin receptor antagonists. Table 1 summarizes the new therapeutic options.

Approaches to treatment

No validated treatment algorithms are available so the recommendations below are based on current guidelines discussed in more detail in the following section. In patients presenting with IBS symptoms of abdominal pain associated with altered stool form or frequency and no alarming findings in the clinical history and physical examination, little diagnostic testing may be needed beyond application of the internationally developed symptom based Rome diagnostic criteria.[139]

Additional diagnostic tests are sometimes warranted to rule out other causes of pain, diarrhea, or constipation. Although not reliably associated with disease, clinical features that may warrant additional testing include hematochezia, nocturnal symptoms, fever, weight loss, or family history of colon cancer or other gastrointestinal disease.

Basic blood tests such as a complete blood count, metabolic profile, and thyroid testing may be useful screening tests, particularly in patients over 50 years and those with a change in symptom pattern. Stool microbiology studies may be warranted in those with symptoms suggestive of infection, such as fever or recent travel history. In people with diarrhea, serologic testing for celiac disease and sigmoidoscopy or colonoscopy with biopsies for microscopic colitis may be warranted. Patients with constipation and features of a defecation disorder (such as straining, sensation of incomplete evacuation, perineal splinting, abnormal dynamic rectal examination[140]) may need to be referred for anorectal manometry testing. People over 50 years should undergo colonic evaluation for cancer. Food allergy testing is controversial and its practice has not been clearly supported.[44 45]

Table 2 | Recommendations for the treatmenet of IBS from National Institute for Health and Care Excellence (NICE), American College of Gastroenterology (ACG), and American Gastoenterological Association (AGA)

Therapy	NICE[142]	ACG recommendation[92]	ACG (quality of evidence)[92]	AGA[141]
Specialized diets	N/A	Weak	Very low	N/A
Fiber	Recommends soluble fiber	Weak	Moderate	N/A
Probiotics	Should not be discouraged	Weak	Low	N/A
Peppermint oil	N/A	Weak	Moderate/Low	N/A
Loperamide	Recommends as first line therapy	Strong recommendation against	Very low	Very low
Polyethylene glycol	Recommends	Weak	Very low	Low
Antispasmodics	Recommends as first line	Weak	Low	Low
Antidepressants	Recommends as second line	Weak	High	Low
			Very low	
Psychological Interventions	Recommends in refractory patients	Weak	High	N/A
Alosetron (US only)	N/A	Weak recommendation in women with IBS-D	Moderate	Moderate
5-HT_4 agonists/5-HT_3 antagonists	N/A	Strong recommendation against	Low	N/A
Linaclotide	N/A	Strong	High	High
Lubiprostone	N/A	Strong	Moderate	Moderate
Rifaximin	N/A	Weak	Moderate	Moderate
			Very low	

5-HT=5 hydroxytriptamine; IBS-D= diarrhea predominant irritable bowel syndrome; N/A=not applicable.

At presentation most patients with IBS should be provided with education on the central and gastrointestinal mediated mechanisms that contribute to their symptoms, as well as the dietary and lifestyle features, including exercise and stress, that can mediate symptoms.

Patients and physicians should carry out a basic review of the diet to identify potential triggers, such as consumption of caffeine or poorly digested or absorbed carbohydrates such as fructose (for example, corn syrup) or sugar-free foods that contain sorbitol or xylitol. Severe dietary restriction should not be encouraged in most patients; rather, symptoms should be balanced against nutrient needs.

In those with a partial or no response to these initial lifestyle changes, more intensive dietary modification—including a trial of eliminating specific food items or a low FODMAP diet—could be considered. In addition, over-the-counter supplements such as probiotics or Iberogast could be considered. For those with ongoing symptoms despite lifestyle modifications, additional therapies may be needed. The prescribing physician should tailor treatment to the patient's preferences, local availability of non-pharmacological and pharmacological options, and severity of symptoms.

Guidelines

Comprehensive reviews and evaluations of established treatments and newer recommended strategies in IBS are now available. These include the 2014 American College of Gastroenterology (ACG) Monograph on the Management of Irritable Bowel Syndrome,[92] the 2014 American Gastroenterological Association (AGA) Institute Technical Review on the Pharmacological Management of Irritable Bowel Syndrome,[141] and the 2008 National Institute for Health and Care Excellence (NICE) guidelines from the United Kingdom.[142] Table 2 summarises these three reviews.

The ACG monograph was based on meta-analyses that compared each therapeutic class with placebo or no therapy and application of GRADE (Grading of Recommendations Assessment Development and Evaluation System) criteria.[92] The meta-analyses evaluated randomized controlled trials in adults of active intervention versus placebo or no therapy for at least one week and reported a global assessment of improvement in IBS. The GRADE quality assessment generated assessments summarizing the quality of evidence (confidence in effect estimates) into four categories: very low, low, moderate, and high. The literature quality assessment was then combined with four other GRADE criteria (applicability to all patient groups, benefit-risk balance, patient preferences, and cost) to generate a summary recommendation of strong or weak.

Four drug or drug classes received a strong recommendation:

- Insufficient evidence to recommend loperamide for IBS
- Mixed 5-HT_4 agonists and 5-HT_3 antagonists (for example, cisapride, renzapride, and mosapride) are no more effective than placebo for IBS-C
- Linaclotide is superior to placebo for IBS-C
- Lubiprostone is superior to placebo for IBS-C.

The remaining drugs or drug classes received weak recommendations. The numerous weak recommendations probably reflect the use of stringent GRADE criteria, which favor newer studies that incorporate the evidence based study design requisites, larger studies, and studies of single drugs over studies of drug classes. The weak recommendations may also reflect the heterogeneity of IBS symptoms when global outcomes are predominantly assessed, rather than specific symptoms such diarrhea or constipation. The ACG evaluations of treatments for chronic constipation can be found in the full monograph.

The American Gastroenterological Association Institute Technical Review on the Pharmacologic Management of Irritable Bowel Syndrome specifically assessed studies of adults with IBS that compared linaclotide, lubiprostone, polyethylene glycol, rifaximin, alosetron, loperamide, tricyclic antidepressants, selective serotonin reuptake inhibitors, and antispasmodics with placebo.[141]

QUESTIONS FOR FUTURE RESEARCH

Does gluten have an independent effect on digestive symptoms and, if so, what is the underlying mechanism?

Are there specific strains of bacteria that cause or are associated with the symptoms of irritable bowel syndrome (IBS)? Can colonization by these strains be modified through dietary manipulation, probiotic consumption, or fecal infusions on a temporary or permanent basis?

Are there subtypes of IBS with different underlying mechanisms that could be identified and treatment tailored to each subtype?

Why are placebo response rates in IBS clinical trials so high? How much can be attributed to positive thinking, natural fluctuations in symptoms, participant selection bias, or biased responses?

How much do lifestyle factors and practices such as exercise, sleep, and stress management affect IBS symptom severity?

Methods for deriving focused clinical questions and subsequently reviewing and rating the quality of the evidence were based on the GRADE criteria, similar to the ACG monograph.[92] Only critical and important outcomes, as defined in the GRADE criteria approach, were summarized, and when available the FDA responder outcome was considered a critical outcome. For pharmacologic treatments of IBS, the authors defined the lowest clinically meaningful improvement as 10%. Linaclotide was the only treatment with a high level of evidence. Drugs with moderate quality evidence were alosetron, lubiprostone, and rifaximin, and those with low quality evidence were loperamide, polyethylene glycol, antispasmodics, and antidepressants.

The 2013 NICE guideline comprehensively reviewed the diagnosis and management of IBS in adults in primary care.[142] Recommendations were based on a systematic review, and where evidence was lacking, the guideline development group's opinion was taken into account. NICE recommends:

- Strongly supporting self help (general lifestyle, activity, and diet)
- Reviewing and, where appropriate, decreasing fiber intake to 12 g/day or increasing soluble fiber consumption
- Titrating doses of laxatives or antimotility agents to Bristol stool form type 4
- Using laxatives, loperamide, or antispasmodics as first line treatment for pain and discomfort and tricyclic antidepressants as second line
- Considering psychological interventions in those with symptoms greater than 12 months that are refractory to conventional treatments
- Not discouraging the use of probiotic products for at least four weeks
- Considering referral to a dietitian for dietary recommendations if diet is a major contributor.

Overall, the three guidelines showed reasonable agreement, although some disparity was seen. Disagreement came from the NICE guidelines being geared towards primary care and being based in part on group opinion, whereas the ACG and AGA reviews were assessments of the quality of the literature based on GRADE methodology, which is a reflection of the quality of trials and less directly an assessment of the treatment itself. Furthermore, the ACG monograph focused on one primary clinical outcome of global IBS improvement (a binary measure), whereas the AGA review evaluated two to five clinical outcomes.

Conclusions

Irritable bowel syndrome is a heterogeneous disorder that is the consequence of a complex bidirectional interaction between the brain and gut.[143] Current management aims to reduce symptoms and, equally importantly, improve health related quality of life. With the growing number of treatment options, we recommend an individualized approach, which should take into account the value of structured patient education and other non-pharmacologic strategies. It is important to set patients realistic goals to prevent dissatisfaction with the chronic nature of the disorder. It is also important to reassure patients and provide them with hope by discussing emerging therapies, which may reduce the future impact of IBS.

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