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# Irritable bowel syndrome: new and emerging treatments

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## 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 (box).

IBS can be clinically subtyped into IBS with constipation (IBS-C), IBS with diarrhea (IBS-D) and mixed IBS (IBS-M).

## Epidemiology

Global estimates of prevalence vary from 5% to 15%.<sup>2-5</sup> 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. Women are more likely than men to seek medical attention for the condition and to report IBS-C,<sup>7</sup> whereas IBS-D is more common in men.<sup>6</sup> The prevalence of IBS decreases with increasing age, and new onset of symptoms after 50 years is uncommon.<sup>5</sup>

IBS clearly affects patients' quality, but not quantity, of life.<sup>8-11</sup> 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.<sup>13</sup>

## Overview of conventional treatments

### Non-pharmacological

Several non-pharmacological therapies exist for IBS, including structured patient education,<sup>35 36</sup> dietary manipulation,<sup>37</sup> and stress management.<sup>ENREF\_1.38-40</sup> Patient education can

### Rome III diagnostic criteria for irritable bowel syndrome (IBS) and subtypes<sup>1</sup>

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

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.

## Pharmacological

Over the counter treatments include fiber supplements, simeticone, lactase enzyme tablets, digestive aids (such as  $\alpha$ -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.

## New non-pharmacological treatments

### Dietary therapies

Patients often report dietary triggers for their symptoms, although no specific food item has been conclusively implicated in the pathogenesis of IBS.<sup>41 42</sup> 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.<sup>43</sup>

Studies of exclusion diets, including dairy and wheat, have yielded conflicting results. Food allergy testing for IBS is therefore highly controversial and is not advocated by most academic experts and clinicians.

### Fermentable carbohydrates

Several recent retrospective and prospective studies have suggested that a diet low in fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAPs) is beneficial.<sup>47-51</sup> 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.<sup>42</sup> Figure 1 provides a list of low and high FODMAP foods.

Two prospective, randomized trials report positive findings but 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.<sup>53</sup> Because patients often request dietary guidance from their providers, a low FODMAP diet could be cautiously considered for

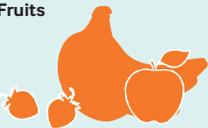
Food category	Low FODMAP examples	High FODMAP examples
<b>Dairy products</b> 	<ul style="list-style-type: none"> <li>Lactose-free dairy products</li> <li>Hard cheeses</li> </ul>	<ul style="list-style-type: none"> <li>Ice cream</li> <li>Milk (including goats' milk)</li> <li>Soft cheeses (camembert/brie)</li> <li>Yoghurt</li> <li>Cream</li> </ul>
<b>Vegetables</b> 	<ul style="list-style-type: none"> <li>Bean sprouts, bok choy</li> <li>Capsicum, carrots, celery, cucumber, corn</li> <li>Eggplant, lettuce, leafy greens</li> <li>Pumpkin, potatoes</li> <li>Tomatoes, zucchini, all fresh herbs</li> </ul>	<ul style="list-style-type: none"> <li>Artichokes, asparagus</li> <li>Beetroot, broccoli, brussel sprouts</li> <li>Cabbage, cauliflower, fennel, green beans, garlic</li> <li>Mushrooms, okra, onions</li> <li>Snow peas, squash</li> </ul>
<b>Fruits</b> 	<ul style="list-style-type: none"> <li>Bananas, berries, cantaloupe melon</li> <li>Grapes, grapefruit, honeydew melon, kiwi</li> <li>Lime, passion fruit, pineapple</li> <li>Rhubarb, all citrus fruits</li> </ul>	<ul style="list-style-type: none"> <li>Avocado, apples, apricots</li> <li>Cherries, dates, dried fruits, figs</li> <li>Mango, nectarines</li> <li>Papaya, peaches, pears, plums, prunes</li> <li>Watermelon</li> </ul>
<b>Meats and protein sources</b> 	<ul style="list-style-type: none"> <li>Fish, meat, chicken, tofu, shellfish, eggs</li> </ul>	<ul style="list-style-type: none"> <li>Legumes, pulses</li> </ul>
<b>Breads and cereal</b> 	<ul style="list-style-type: none"> <li>Spelt and gluten-free bread</li> <li>Rice cereal, rice quinoa, gluten-free pasta</li> </ul>	<ul style="list-style-type: none"> <li>Wheat and wheat based bread</li> <li>Cereals, rye, wheat, pasta</li> </ul>
<b>Food additives, spices, and condiments</b> 	<ul style="list-style-type: none"> <li>Most spices and herbs</li> <li>Mayonnaise</li> <li>Olives, onion powder, olive oil, pepper, salt</li> <li>Maple syrup without high fructose corn syrup, mustard</li> <li>Soy sauce, chili sauce</li> <li>Sugar</li> <li>Vinegar (including balsamic vinegar)</li> </ul>	<ul style="list-style-type: none"> <li>Any food with high fructose corn syrup or agave syrup content</li> <li>Artificial sweeteners including sorbitol, mannitol, isomalt, xylitol (cough drops, gums, mints)</li> <li>Chutneys, coconut, honey, jams, jellies</li> <li>Molasses, pickles, relishes</li> </ul>

Fig 1 | Low and high FODMAP (fermentable oligosaccharides, disaccharides, monosaccharides, and polyols) containing food

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. The concept of immune-mediated non-celiac gluten sensitivity has been proposed.<sup>18</sup> 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).<sup>54</sup> 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.<sup>55 56</sup> 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.<sup>57</sup> They were subsequently randomized to a high gluten, low gluten, or control 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

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 found a significant benefit of soluble fiber in global IBS symptoms.<sup>58</sup>

### Exercise

Because exercise improves gas transit and defecatory patterns, a potential benefit in IBS is plausible.<sup>62</sup> Furthermore, regular exercise may reduce stress and affect visceral hyperalgesia through central pathways.<sup>19</sup>

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.<sup>63</sup>

### Biofeedback therapy for IBS-C

Many patients with IBS-C, and some without constipation, describe difficulty with evacuation.<sup>64</sup>

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.<sup>69</sup> Biofeedback therapy was successful 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.

### 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,<sup>70-72</sup> it has been proposed that manipulation of the microflora by probiotics may be therapeutic. 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.<sup>73-78</sup> The general consensus is that probiotics show modest benefit, with an estimated number needed to treat of 4. However, the real estimate of probiotic efficacy remains to be determined.

### Herbal therapies

#### 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.

A review published in 2013 assessed data on the safety and efficacy of STW 5 in functional gut disorders including IBS.<sup>87</sup> Of the 12 studies in the review, two specifically looked at IBS, but only one was randomized and placebo controlled.<sup>82</sup> An intention to treat analysis showed that

## 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.

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.

### 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.<sup>88</sup> 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).

### CNS based therapy

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.<sup>93</sup>

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.

Figure 2 provides an overview of current treatments for IBS.

## 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,<sup>20 72</sup> and in IBS related small intestinal bacterial overgrowth.<sup>94</sup>

Neomycin and metronidazole have been studied in single RCTs in patients with IBS and have shown varying efficacy.<sup>102 103</sup> 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.<sup>107</sup> This review also found comparable rates of adverse events for rifaximin and placebo.

### Pharmacotherapy for IBS-D: serotonin receptor antagonists

A randomized crossover trial published in 2013 assessed whether ondansetron, a 5HT<sub>3</sub> receptor antagonist traditionally used for nausea and vomiting, would be useful because of its constipating effect.<sup>111</sup> 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 ( $P=0.002$ ). 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);  $P=0.001$ ).

### Pharmacotherapy for IBS-C

#### Chloride channel activators

Newer prescription drugs for IBS-C include laxatives such as lubiprostone. 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 signifi-

cantly greater improvements in mean abdominal discomfort and pain scores ( $P=0.039$ ).<sup>113</sup> 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.

#### 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.

Three large randomized, double blind, multicenter, placebo controlled studies have assessed linaclotide.<sup>116 117</sup> 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.<sup>118</sup>

#### Summary of emerging treatments

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.

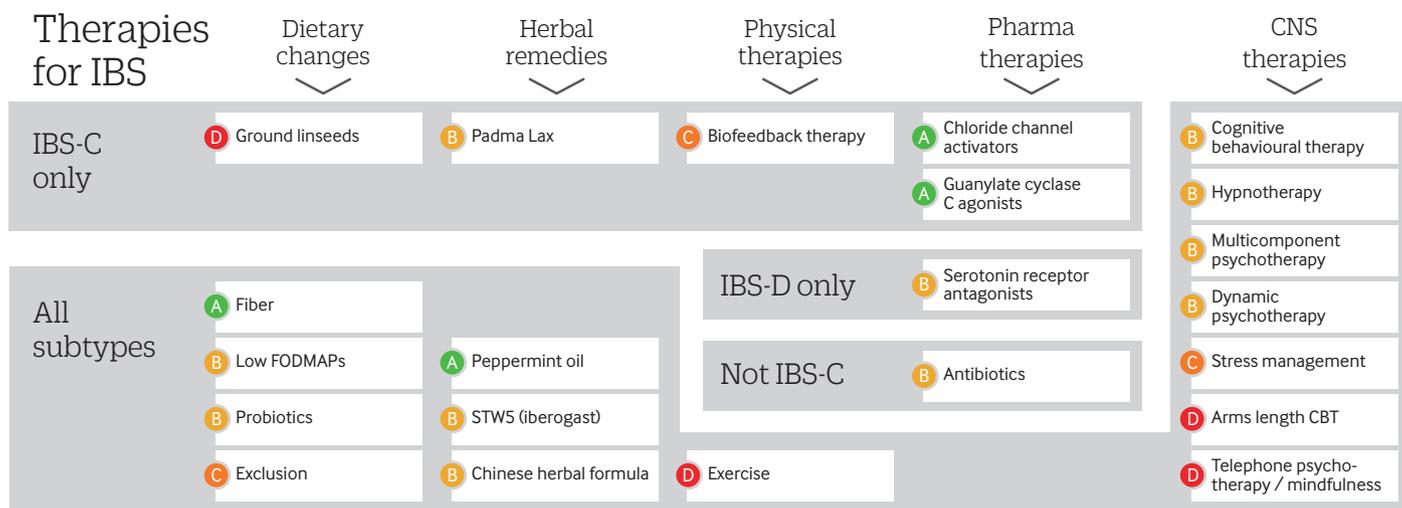
### Approaches to treatment

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.<sup>139</sup>

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 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.<sup>44 45</sup>

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.



The grades of recommendation used in this graphic are based on the Oxford Centre for Evidence-based Medicine System (March 2009). A = Directly based on high quality RCTs, B = cohort studies / low-quality RCTs, C = case-control studies, D = poor quality / inconsistent studies. Full details available at: <http://www.cebm.net/>

Fig 2 | Overview of current treatments for IBS. View the interactive graphic: [www.bmj.com/content/350/bmj.h1622/infographic](http://www.bmj.com/content/350/bmj.h1622/infographic)

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. Table 2 on thebmj.com summarises these three reviews.

The 2013 NICE guideline comprehensively reviewed the diagnosis and management of IBS in adults in primary care.<sup>142</sup> 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 antispasmodic 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.

Table 1 | Selected new treatments for IBS\*

Treatment	Dosing and administration	Comments on effect	NNT
Exercise <sup>63</sup>	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 <sup>69</sup>	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) <sup>78</sup>	Magnitude of benefit and the most effective species and doses remain uncertain	4
Iberogast (STW-5) <sup>87</sup>	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 <sup>107</sup>	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 <sup>114</sup>	8 µg twice daily (prescription only)	IBS-C patients on lubiprostone endorsed greater symptom relief (17.9% v 10.1%)	12
Linaclotide <sup>117</sup>	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.