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CLINICAL REVIEW

Irritable bowel syndrome

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Irritable bowel syndrome (IBS) is one of the commonest gastrointestinal conditions encountered in primary or secondary care. The disorder is more common in younger people, and women. The diagnosis should be reached using symptom based clinical criteria, rather than excluding underlying organic disease by exhaustive investigation. There is no single known unifying cause, but biological markers have been identified. Treatment should be directed towards relief of the predominant symptom (or symptoms) reported, although these may change over time. Since there is no medical therapy established to alter the natural history of IBS in the longer term, the disorder represents a considerable financial burden to the health service, owing to medical consultations and the consumption of other valuable resources. Since the publication of management guidelines from the National Institute for Health and Clinical Excellence in 2008,[w1] there have been some significant developments in terms of synthesis of existing evidence, as well as emerging therapies. We therefore summarise recent systematic reviews, meta-analyses, and randomised controlled trials in order to provide a general update as to how to effectively identify and manage this disorder.

What is IBS and who gets it?

IBS is a chronic functional disorder of the lower gastrointestinal tract. Characteristic symptoms are abdominal pain or discomfort in association with the onset of either an alteration in stool form or frequency. Other symptoms such as the relief of pain or discomfort by defecation, or abdominal bloating are considered supportive of the diagnosis. The current classification system for the functional gastrointestinal disorders, the Rome criteria,[w2] further subdivides patients with IBS according to the predominant stool type produced. Thus, patients are classed as diarrhoea predominant (IBS-D), constipation predominant (IBS-C), or mixed (IBS-M), where stool type fluctuates between diarrhoea and constipation. Some patients cannot be classified, and the predominant stool type often changes with time.[w3]

Population based studies have shown that the prevalence of symptoms compatible with IBS in the community varies from around 5% to more than 20%. A recent systematic review of 80 cross sectional surveys in the community confirmed that prevalence varied considerably with geography, with a pooled prevalence of 7% in South East Asia, 12% in northern Europe and North America, and 21% in South America.[1] According to predominant stool form, IBS-D was the commonest subtype, with a pooled prevalence of 40%, and IBS-M the least common, with a pooled prevalence of 23%. The odds of IBS were significantly lower in people aged 50 years or more than in those under 50 years. Few studies provided data concerning the effect of socioeconomic status on prevalence of IBS. There was a female preponderance, with a pooled odds ratio of 1.67 for IBS in women versus men.[2] Women with IBS were more likely to show IBS-C (odds ratio 2.38) and less likely to meet criteria for IBS-D (0.45) than men with IBS. Longitudinal follow-up studies suggest that IBS does not adversely affect survival in the community.[w4 w5]

What is the underlying pathophysiology of IBS?

There is no single unifying cause to explain the symptoms that sufferers report. However, numerous mechanisms have been proposed (fig⇓). Presence of IBS is associated with increased levels of psychiatric distress, and maladaptive coping strategies.[w6] The condition aggregates in families,[w7] probably due to a combination of genetics and shared upbringing. Patients with IBS show abnormal small bowel and colonic transit compared with healthy controls, suggesting that changes in stool form or frequency could relate to disturbed gastrointestinal motility.[w8] The abdominal pain or discomfort could be due to a combination of an abnormal stimulus (for example, excessive gas production), visceral hypersensitivity, and abnormal central pain processing. Balloon distension of the gastrointestinal tract in patients leads to pain at lower thresholds than in those who do not have the disorder,[w9] as well as stimulating higher levels of brain activity in the regions associated with pain modulation and emotional arousal.[w10] Some investigators have reported

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Web appendix: Web references

Summary points

- Irritable bowel syndrome (IBS) affects up to one in five people at some point in their lives
- The condition is commoner in younger people and women, and is not associated with increased mortality
- A positive diagnosis of IBS should be reached using symptom based clinical criteria, not after excluding organic disease by exhaustive investigation
- Exclusion diets (for example, low levels of fermentable oligosaccharides, disaccharides, monosaccharides, and polyols) and exercise may be of benefit
- Soluble fibre, antispasmodics (including peppermint oil), antidepressants, agents acting on the 5-HT receptor, rifaximin, and probiotics are all more effective than placebo for treating IBS
- Psychological therapies should be reserved for patients failing these treatments

Sources and selection criteria

We searched Medline, Embase, the Cochrane Database of Systematic Reviews, and Clinical Evidence online using the search term "irritable bowel syndrome," as well as recent conference proceedings. We limited studies to those conducted in adults, and focused on systematic reviews, meta-analyses, and high quality randomised controlled trials published within the past five years, wherever possible.

perturbations of the gastrointestinal flora in patients.[w11] Chronic, low grade inflammation of the gastrointestinal mucosa, perhaps driven by inappropriate mast cell activation, has also been implicated as a potential aetiological factor.[w12] Biomarkers have been identified in the serum of some patients,[w13 w14] but are of uncertain significance.

How is IBS diagnosed?

In a patient without lower gastrointestinal alarm symptoms (box) who has longstanding typical symptoms of IBS (intermittent abdominal pain or discomfort associated with an erratic bowel habit, and often bloating), the diagnosis should be made on clinical grounds, without the need for recourse to invasive investigations. Symptom based diagnostic criteria facilitate this approach, which include the Manning criteria and the Rome criteria (table⇓).[w2 w15] There have been three iterations of the Rome criteria to date, and the Rome III criteria are the current accepted diagnostic standard used among gastroenterologists for diagnosing IBS in clinical practice, as well as for recruiting patients into treatment trials for the disorder.

However, a recent systematic review and meta-analysis of observational studies, all of which were conducted in secondary care, showed that these criteria have not been validated extensively, and do not predict IBS with any great accuracy.[3] The Manning criteria, which had been validated in four studies, yielded pooled positive and negative likelihood ratios of 2.9 and 0.29, respectively. The first iteration of the Rome criteria had been validated in only one study (positive likelihood ratio 4.8, negative 0.34), and the Rome III criteria had not been validated at all. These differences may be of little relevance in primary care, where few physicians are familiar with these criteria or use them to make a diagnosis of IBS, yet can still diagnose the condition accurately using a symptom based approach.[w16] Longitudinal follow-up in patients with a positive diagnosis of IBS suggests that the development of subsequent organic disease is rare.[w17] Therefore, diagnostic testing is generally reserved for those with alarm features. No evidence supports undertaking a routine panel of blood tests,[w18] although clinicians often order tests such as a full blood count and C reactive protein. However, serological testing to exclude coeliac disease is probably worthwhile,[4] and is cost effective if the prevalence of coeliac disease among patients with suspected IBS is around 5%.[w19] An effective and empathetic doctor-patient relationship is essential once the diagnosis is reached, and is associated with increased patient satisfaction and reduced consultations.[w17]

What are the treatment options?

Diet and lifestyle

Theoretically, fibre should increase transit time in patients with IBS, but its role as a therapy remains controversial. A Cochrane review, updated recently, identified 12 randomised controlled trials of fibre, all conducted in secondary or tertiary care.[5] This review suggested no benefit for either soluble or insoluble fibre. However, another meta-analysis of the same trials showed that soluble fibre, used in six trials in the form of ispaghula, significantly improved symptoms compared with placebo, with a number needed to treat to prevent one patient with IBS remaining symptomatic of six.[6] This disparity in findings between meta-analyses probably results from the use of different endpoints to pool data when judging treatment success.[w20] The Cochrane review pooled data from eligible trials according to the effect of fibre on abdominal pain or global IBS symptoms separately, whereas the second meta-analysis pooled data for both endpoints together. Adverse events were rare. A recent high quality trial conducted entirely in primary care also showed a significant benefit of ispaghula over placebo.[7]

Patients with IBS may report certain foodstuffs that trigger symptoms. In a randomised controlled trial conducted in tertiary care that performed IgG testing for foods, and which allocated patients to an elimination diet based on the results or a sham diet, symptom scores were significantly lower among patients receiving the elimination diet.[8] More recently, interest in the potential role of fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAPs) in generating symptoms in IBS, via their fermentation and osmotic effects, has led to proposals of low FODMAP diets as a treatment. Foods with high levels of FODMAPs include some fruits (apples, cherries, peaches, and nectarines) artificial sweeteners, most lactose-containing foods, legumes, and many green vegetables (broccoli, Brussels sprouts, cabbage, and peas). In a crossover trial that switched 15 patients with IBS recruited in secondary care from diets that were either low or high in FODMAPs, symptoms such as abdominal pain or discomfort, bloating, and flatus were all significantly worse during the high FODMAP diet.[9] Evidence from a double blind, placebo controlled trial also suggests that a gluten free diet may benefit people with IBS who test negative for coeliac disease, with poorer control of symptoms among those randomised to gluten.[10]

Exercise has been shown to improve symptoms in fibromyalgia and chronic fatigue syndrome, both of which may coexist with IBS. In a recent randomised controlled trial, 102 patients with IBS in secondary or tertiary care were instructed to increase

Box: Lower gastrointestinal alarm symptoms

- ≥50 years with no previous colon cancer screening
- Family history of colon cancer
- Weight loss
- Rectal bleeding
- Recent change in bowel habit
- Abdominal mass
- Iron deficiency anaemia
- Haem positive stool

their physical activity for 12 weeks, or to maintain current activity.[11] Patients allocated to increased physical exercise showed significant improvements in scores of IBS symptom severity compared with scores at baseline, while those who maintained current levels of activity were more likely to have worsening of their symptoms compared with the physical activity group.

Patient education also seems to provide some benefit. In one tertiary care study that administered a group education programme to a series of patients with IBS, resolution of symptoms was significantly commoner among attendees of the class, compared with non-attendees.[12] Advocating sleep hygiene helps patients with fibromyalgia, but whether this approach is also useful in IBS is unclear. However, evidence from a small randomised controlled trial conducted in tertiary care suggests that melatonin leads to significantly higher symptom response rates in women with IBS than placebo.[13]

Placebo

The placebo response rate in IBS is high. A meta-analysis of 73 randomised placebo controlled trials in IBS showed a pooled placebo response rate of almost 40%.[14] A recent trial conducted in tertiary care recruited and randomised 80 patients to either open label placebo, which they were told had "beneficial effects through mind-body self-healing processes," or no treatment.[15] Almost 50% of patients assigned to placebo reported adequate relief of symptoms, which was significantly higher than with no treatment. The authors suggested that this novel strategy allows the ethical use of placebo as a treatment, without the need for deception of the patient, which would otherwise undermine the patient-doctor relationship.

Antispasmodic drugs

Most antispasmodic drugs compete with acetylcholine at postganglionic parasympathetic nerve endings, inhibiting smooth muscle contraction. Peppermint oil also has antispasmodic properties, bringing about smooth muscle relaxation via calcium channel blockade. These drugs could therefore have beneficial effects on abdominal pain or discomfort. The efficacy of antispasmodics has been confirmed in two recent meta-analyses,[5 6] but both had substantial heterogeneity between randomised controlled trials, and none of the trials identified was conducted entirely in primary care. In one meta-analysis of 22 randomised controlled trials,[6] the number needed to treat was five, and when the efficacy of individual antispasmodics was studied, otilonium, cimetropium, hyoscine, pinaverium, and dicycloverine were all more effective than placebo. Adverse events were summarised in one meta-analysis,[6] and were significantly commoner with active therapy, with a number needed to harm of 17.5. Data from four placebo controlled trials of peppermint oil, all conducted in secondary care, were pooled in one of these meta-analyses.[6] The number needed to treat to prevent one patient with IBS remaining symptomatic was 2.5. Adverse events were rare.

Antidepressants

Patients with IBS show higher levels of anxiety and depression than controls without IBS. Antidepressants are an effective therapy in chronic pain conditions, and alter gastrointestinal transit time. Evidence from two meta-analyses suggests that antidepressants are of benefit in IBS.[5 16] Both tricyclic antidepressants and selective serotonin reuptake inhibitors were more effective than placebo for the treatment of IBS. Again, none of the trials identified was conducted in primary care. When data from nine randomised controlled trials of tricyclic antidepressants were pooled, the number needed to treat was four, with no heterogeneity detected between studies. Selective serotonin reuptake inhibitors also showed a benefit, in five randomised controlled trials, with a number needed to treat of 3.5, but with significant heterogeneity between studies. Adverse events were not significantly commoner with antidepressants in the pooled trials,[16] but there remains a risk of harm with this class of agents.

Agents acting on the 5-hydroxytryptamine (5-HT) receptor

This class of drugs has the potential to ameliorate the smooth muscle spasm, abdominal pain, and change in bowel habit of patients with IBS. Alosetron, a 5-HT_3 receptor antagonist, is licensed in the United States only for female patients with severe IBS-D. A meta-analysis of eight placebo controlled trials conducted in secondary or tertiary care showed a number needed to treat of eight, albeit with significant heterogeneity between studies.[17] However, the drug was associated with several cases of ischaemic colitis and severe constipation, and its use is now restricted by a prescribing programme from the US Food and Drug Administration. Prucalopride is a highly selective 5-HT_4 agonist, and is effective for the treatment of chronic idiopathic constipation, with a number needed to treat of six.[18] It has yet to be tested in IBS, but theoretically should be of benefit in IBS-C.

Antibiotics and probiotics

In view of the proposed abnormalities of gastrointestinal flora in patients with IBS, antibiotics have the potential to modulate the bacterial composition of the gastrointestinal tract and alter the natural history of IBS in the short term. The non-absorbable antibiotic rifaximin has recently been tested in two large placebo controlled trials conducted in secondary and tertiary care in North America.[19] More than 1200 patients with IBS were randomised to two weeks of therapy, with follow-up at 12 weeks. Overall, adequate relief of global IBS symptoms and bloating were significantly more likely with rifaximin at four week follow-up; this effect seemed durable, being maintained

at 12 weeks. Adverse events were no commoner with rifaximin and, importantly, there were no cases of *Clostridium difficile*.

Probiotics are live or attenuated bacteria, or bacterial products, which, when ingested, have beneficial effects. There is evidence to suggest that some probiotics have anti-inflammatory properties or ameliorate visceral hypersensitivity. These effects could theoretically lead to an improvement in symptoms of IBS. A recent meta-analysis identified 18 randomised controlled trials that compared various probiotics with placebo.[20] Five of these trials were conducted in primary care. When data were pooled from the 10 trials that reported dichotomous data, probiotics were superior to placebo, with a number needed to treat of four. However, there was considerable heterogeneity between studies, and different strains and species were used, making it difficult to ascertain which, if any, were of particular benefit; however, a trend was seen towards bifidobacteria improving symptoms. Fifteen trials provided continuous data, with analyses showing that probiotics had a beneficial effect on abdominal pain, and a trend towards a benefit for bloating. Adverse events were rare with active therapy in these trials.

Psychological and behavioural therapies

The rates of psychological disorders, such as anxiety, depression, and bipolar affective disorder are twofold to threefold higher in patients with IBS than in controls without IBS.[w21] There have been numerous randomised controlled trials of psychological and behavioural therapies such as cognitive behavioural therapy, hypnotherapy, and dynamic psychotherapy. Two separate meta-analyses have summarised these therapies.[16 21] A Cochrane review, which pooled continuous data from 25 eligible studies, suggested that these therapies are only marginally superior to no treatment,[21] and the authors questioned the clinical significance of any benefit.

In the second meta-analysis,[16] in which the original trial authors were asked to provide dichotomous data, the number needed to treat when all 20 eligible studies using psychological and behavioural therapies were pooled was four, although there was significant heterogeneity between studies and evidence of publication bias. Only one trial was conducted in primary care. There were benefits for cognitive behavioural therapy, hypnotherapy, multicomponent psychological therapy, and dynamic psychotherapy, but no benefit from relaxation therapy or self administered cognitive behavioural therapy. However, most of the trials assigned patients in the control arm to no treatment, other than joining a waiting list for the active intervention to be administered at study completion. Therefore, there is the possibility of a placebo effect in the active intervention arms, and the efficacy of these therapies may have been overestimated.

Further trials have been published since these two meta-analyses. A recent trial of hypnotherapy conducted in both secondary and tertiary care also showed a significant benefit over supportive treatment (in the form of dietary advice, relaxation training, and information about the pathophysiology of the disorder). This trial included the largest number of patients with IBS to date, but also noted that the efficacy of hypnotherapy was lower in secondary care, suggesting that it may be less reproducible outside of specialist centres.[22] Mindfulness training, which involves focusing on present-moment experience and non-judgmental awareness of body sensations, has also been studied in female patients with IBS.[23] In this tertiary care trial, patients were allocated to mindfulness training or a support group, and followed up for three months. Patients assigned to the active intervention had a significant reduction in severity of IBS symptoms and abdominal pain. Overall, psychological and behavioural therapies are probably of benefit in IBS, but they are time consuming to administer, and are probably best reserved for patients who fail more conventional treatments.

Alternative therapies

In a meta-analysis of 17 secondary and tertiary care based studies, acupuncture seemed to be superior to pharmacological therapy in several randomised controlled trials conducted in China.[24] However, it was no more effective, in terms of symptom improvement, than a sham acupuncture control, suggesting that the improvements observed may be based on Chinese patients' preconceived expectations of the relative efficacy of acupuncture compared to drugs. Herbal therapies such as iberogast (also known as STW 5), which is a combination of various plant extracts, and St John's wort, have also been the subject of placebo controlled trials in IBS,[25 26] with STW 5 showing superiority over placebo, but St John's wort having no beneficial effect. Another trial of Chinese herbal therapy (a combination of 20 different herbs) suggested a benefit in IBS,[w22] but the formula's efficacy remains to be confirmed. In summary, any benefit of herbal therapies remains unclear.

Emerging therapies

Novel therapies for the treatment of IBS are emerging. Lubiprostone and linaclotide are drugs that act locally on chloride channels and guanylate cyclase receptors in the gastrointestinal tract, respectively. Both agents stimulate intestinal fluid secretion and accelerate transit, by increasing chloride concentration within the gastrointestinal lumen. These drugs are effective in the treatment of chronic idiopathic constipation,[18] and have also been tested in IBS-C. Results of two randomised trials conducted in secondary and tertiary care in the US showed significantly higher response rates with lubiprostone than placebo, although the overall effect was modest, with an absolute difference in treatment effect of only 8%.[27] The drug is now approved in the US for the treatment of IBS-C. More recently, the efficacy of linaclotide was studied in over 800 patients, again with response rates significantly greater than placebo.[28] Other emerging therapies include bile acid sequestrants (such as colesevelam), bile acid transporter inhibitors, and pancreatic enzyme supplements, all of which are under investigation,[29 30] although convincing data from randomised controlled trials are currently lacking. These emerging therapies, which may act more selectively on the gastrointestinal tract, have the potential to improve symptoms, perhaps without causing the systemic side effects associated with more traditional pharmacological treatments.

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Tips for non-specialists

- Encourage patients to take regular exercise, and consider exclusion diets, although these diets need good patient compliance and dietitian support
- Try to tailor treatment according to either predominant stool form or the most troublesome symptom reported
- Consider antispasmodics or peppermint oil in patients for pain and diarrhoea, with tricyclic antidepressants as second line therapy
- Consider a soluble fibre supplement (ispaghula) as first line therapy in patients with IBS-C, possibly adding an osmotic laxative, with a trial of selective serotonin reuptake inhibitors as second line therapy
- In patients with bloating or diarrhoea as the predominant symptom consider the use of a probiotic (such as bifidobacteria or rifaximin)
- Consider referral to a specialist if first line or second line therapies are ineffective, or if there is doubt about the diagnosis on the part of either the patient or the physician

Additional educational resources

Resources for healthcare professionals

- Ruepert L, Quartero AO, de Wit NJ, van der Heijden GJ, Rubin G, Muris JW. Bulking agents, antispasmodics and antidepressants for the treatment of irritable bowel syndrome. *Cochrane Database Syst Rev* 2011;10:CD003460
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- Clinical practice guideline. Irritable bowel syndrome in adults: diagnosis and management of irritable bowel syndrome in primary care. February 2008. http://guidance.nice.org.uk/CG61/Guidance/pdf/English

Resources for patients

- Irritable bowel syndrome: NHS choices (www.nhs.uk/Conditions/Irritable-bowel-syndrome/Pages/Introduction.aspx)—a website providing advice on what IBS is, how it is diagnosed, and the treatments commonly used for the disorder
- IBS Network (www.theibsnetwork.org)—a website providing support and advice for people who think they may have IBS, as well as those with an established diagnosis

Questions for future research

- Do antispasmodics or antidepressants have a benefit in patients with IBS in primary care?
- Do patients with IBS derive lasting reassurance following investigation to exclude organic illness?
- How does placebo exert a beneficial effect on IBS symptoms?
- What is the optimal dietary therapy for IBS?

How to discuss IBS and its treatment with patients

- Explain that IBS is likely to be a lifelong disorder, but that the symptoms come and go
- Explain that the cause of IBS is not known
- Explain that increasing soluble fibre, or excluding foods containing high levels of FODMAPs, may improve symptoms without the need for medical treatment
- Mention that increasing exercise levels may also help symptoms
- Where these measures fail and medical treatment is needed, make sure that the patient is aware that most drugs used to treat IBS are safe and well tolerated

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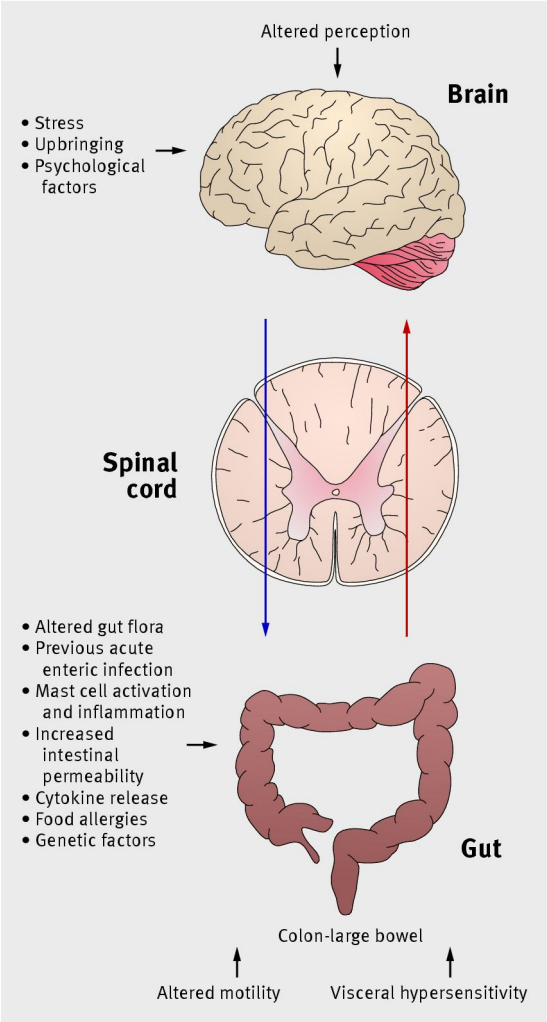
Table

Table 1| Diagnostic criteria for IBS

Criteria (year described)	Symptom items included	Minimum symptom duration required
Manning (1978)[w15]	Any of*: abdominal pain relieved by defecation, more frequent stools with onset of pain, looser stools with onset of pain, passage of mucus per rectum, feeling of incomplete emptying, visible abdominal distension reported by patients	None
Rome III (2006)[w2]	Recurrent abdominal pain or discomfort ≥3 days per month in the past 3 months associated with two or more of: improvement with defecation, onset associated with a change in frequency of stool, onset associated with a change in form of stool	Symptom onset ≥6 months before diagnosis

*No minimum number of symptom items is needed to meet criteria for IBS but, conventionally, the reporting of at least three items by the patient is used to increase specificity.

Figure



Proposed aetiological mechanisms in IBS