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Treating irritable bowel syndrome with probiotics: the evidence

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Irritable bowel syndrome (IBS) is a disorder of chronic abdominal pain, altered bowel habit and abdominal distension. It is the commonest cause of referral to gastroenterologists in the developed world and yet current therapeutic strategies are often unsatisfactory. There is now increasing evidence linking alterations in the gastrointestinal (GI) microbiota and IBS. Changes in faecal and mucosa-associated microbiota, post-infectious IBS, a link with small intestinal bacterial overgrowth and an up-regulation of the GI mucosal immune system all suggest a role for the GI microbiota in the pathogenesis of IBS. Given this evidence, therapeutic alteration of the GI microbiota by probiotic bacteria could be beneficial. The present paper establishes an aetiological framework for the use of probiotics in IBS and comprehensively reviews randomised placebo-controlled trials of probiotics in IBS using multiple electronic databases. It highlights safety concerns over the use of probiotics and attempts to establish guidelines for their use in IBS in both primary and secondary care.

Probiotics: Irritable bowel syndrome: Small bowel intestinal overgrowth: Gastrointestinal microbiota

Irritable bowel syndrome (IBS) is characterised by abdominal pain, bloating and change in bowel habit with an absence of any overt mucosal abnormality[1]. Although IBS affects between 10% and 20% of the population in Europe and the USA[2], its pathogenesis remains poorly understood. Research into the aetiology of IBS has centred on the interaction between the gastrointestinal (GI) tract and the central and enteric nervous system[3]. Novel therapeutic agents such as tegaserod[4], alosetron[5] and more recently corticotrophin-releasing hormone antagonists[6] have been based on this research. This emphasis on dysmotility and visceral hypersensitivity in IBS has shifted the focus away from the GI tract, yet there is increasing evidence of GI immune up-regulation and altered microbiota[7]. This evidence has highlighted the potential for therapeutic manipulation of the GI microbiota in particular with probiotics. Probiotics are defined as 'live microorganisms, which, when administered in adequate amounts, confer a health benefit on the host'[8]. Probiotics have been shown to be efficacious in a number of GI disorders including the treatment of *Clostridium difficile*-associated diarrhoea[9], inflammatory bowel disease[10], acute gastroenteritis[11–13] and necrotising enterocolitis[14]. The present paper describes the reasons for the use of probiotics in IBS and their potential mechanisms of action and summarises the clinical evidence for their use to date. Finally, it aims to synthesise guidance for when and how to use probiotics in IBS populations in both primary and secondary care.

The role of the gastrointestinal microbiota in irritable bowel syndrome

Several factors suggest that the GI microbiota might be important in the pathogenesis of IBS. First, several studies have found differences in the faecal and mucosa-associated microbiota of patients with IBS and healthy controls[15–19]. As a result of the wide range of techniques used, differing patient groups and the complexity of the GI microbiota it is difficult to draw firm conclusions from this series of studies. However, there does appear to be a consistent theme of a relative reduction of the lactobacilli and bifidobacteria[15,17–19] in patients with IBS and higher concentrations of species such as enterobacteriaceae[15,19],

Abbreviations: GI, gastrointestinal; GSS, global symptom score; IBS, irritable bowel syndrome.

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coliforms[15] and bacteroides[18]. However, what is less clear, without a greater understanding of the metabolic and immunological roles of the GI microbiota, is whether these changes are a primary or secondary phenomenon.

In addition to differences in the GI microbiota in IBS there is increasing evidence of an activation of the intestinal immune system in IBS, with studies demonstrating increased concentrations of mucosal intra-epithelial lymphocytes[20,21], mast cells[21–24] and 5-hydroxytryptamine-secreting enterochromaffin cells[20]. Given the evidence for the role of the GI microbiota in the profound inflammatory state in ulcerative colitis and Crohn's disease, luminal antigens such as the microbiota may play a similar role in IBS.

Many of the studies demonstrating an up-regulation of the GI mucosal immune system have been in post-infectious IBS, in which there is a clear infective trigger[20]. A longitudinal study has monitored long-term sequelae following an outbreak of gastroenteritis associated with water contamination in a town in Canada that resulted in >2300 cases of gastroenteritis[25]. Using the unaffected population as controls the study found that over the course of 2 years the OR for developing IBS in the affected population was 4·8 (95% CI 3·4, 6·8; $P<0·001$).

Finally, there is controversial evidence linking small intestinal bacterial overgrowth and IBS. Bloating and flatulence are common symptoms of IBS[26] and bacterial fermentation of undigested carbohydrate leads to production of gases CO_2, H_2 and CH_4. Several studies by the same research group have examined patients with IBS using a lactulose H_2 breath test and have found an increased incidence of small intestinal bacterial overgrowth of approximately 78–84%[27–30]. However, when the incidence of small intestinal bacterial overgrowth is measured using jejunal aspiration and culture (considered to be the gold standard) the incidence has been found to be approximately 4%[31].

There are therefore a number of plausible reasons why the GI microbiota may play a role in the aetiology of IBS. However, some of the best evidence is in the success of modulating the host microbiota either with antibiotics[32,33] or probiotics.

Probiotics in irritable bowel syndrome: mechanisms of action

In order to be of clinical benefit probiotic bacteria must be able to survive GI transit (e.g. gastric acid and bile acid resistance) and then be able to demonstrate functional efficacy[8]. There is substantial evidence demonstrating that probiotic bacteria can interact with the host GI mucosal immune system[34–36]. Given the evidence demonstrating an increase in immune cell populations in IBS, it is probable that immunomodulation by probiotics is a key constituent of their mechanism of action. A trial of the probiotic bacteria *Bifidobacteria infantis 35624* has found that at baseline patients with IBS have a higher pro-inflammatory IL-12:anti-inflammatory IL-10 than healthy controls[37]. Administration of the trial probiotic but not placebo reverses these ratios to the levels of the healthy controls. As discussed later, these findings correlate with clinical benefit.

Specific probiotic bacteria appear to directly modulate intestinal pain. *Lactobacillus acidophilus* has been shown to up regulate μ-opioid and cannaboid receptors in colonic epithelial cell lines and in the colonic epithelium in pre-treated rats and mice[38]. Using a rat stress model of visceral hypersensitivity pretreatment with the probiotic was found to ameliorate pain. Similarly, *Lactobacillus paracasei* attenuates abdominal pain and mucosal inflammation in an antibiotic-induced murine model of visceral hypersensitivity[39].

Probiotics have also been shown to alter the integrity of the GI mucosa. The probiotic VSL#3® (a combination of nine strains of various bifidobacteria, lactobacilli and *Streptococcus thermophilus*; VSL Pharmaceuticals, Inc., Gaithersburg, MD, USA) has been shown to induce mucin production in the colon via up-regulation of the gene *MUC2*[40], thereby increasing barrier protection. In addition, as part of a randomised controlled trial of a probiotic drink containing *S. thermophilus*, *Lactobacillus bulgaricus*, *L. acidophilus* and *Bifidobacterium longum* in patients with diarrhoea-predominant IBS, intestinal permeability was analysed[41]. A significant improvement was found in global symptom score (GSS; patient rating of overall improvement in symptoms post-treatment *v.* pretreatment[42]), which was correlated with a significant decrease in small intestinal permeability (measured by lactulose:mannitol urinary excretion; 0·038 *v.* 0·024; $P<0·004$). Interestingly, no change in colonic permeability was found when measured by sucralose urinary excretion, suggesting that the effects are specific to the small bowel. As several studies have shown increased GI permeability in IBS[43,44], therapies that improve barrier function may alleviate symptoms via this mechanism. Although understanding of the exact mechanism of probiotic bacteria is not complete, these examples do provide plausible examples of their efficacy. The data highlight that these effects are often highly species or strain specific and it is therefore important that data from one probiotic are not extrapolated to another.

Probiotics in irritable bowel syndrome: clinical trials

There have now been numerous trials that have investigated the therapeutic benefit of probiotics in IBS, with heterogeneity in dosing regimens, species used and clinical end points. More recently, there have been two systematic reviews[45,46] and two meta-analyses[47,48]. Table 1 summarises the important randomised controlled trials over the last 10 years, highlighting the species used, the trial design and results. Several trials have been excluded from this list because of failure to compare with placebo[49], re-analysis of old data[50], unclear end points[51] or the use of multiple interventions[52]. Many early studies were small single-centre trials[53–57], although more recently a number of much larger multi-centre trials have been undertaken, reflecting the growing interest in the area[58–61].

Lactobacillus plantarum

There are three small single-centre studies using a liquid form of *Lactobacillus plantarum* in IBS. Two studies show

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Table 1. Summary of recent randomised controlled trials of probiotics in irritable bowel syndrome (IBS)

Reference	*n*	Intervention and daily dose	Duration (weeks)	Result
Kajander *et al.*[65]	103	*L. GG, L. rhamnosus LC705, B. breve Bb99, Propionibacterium freudenreichii* spp *shermanii* JS	26	Significant reduction in GSS ($P<0·015$)
Kim *et al.*[54]	48	VSL#3; 10^{11}	4	Failed to show improvement in bloating scores (PEP; $P<0·19$) Reduction in flatulence scores ($P<0·01$)
Bausserman *et al.* [53].	50	*L. GG*; 10^{10}	6	PEP defined as resolution of pain; failed to show benefit treatment arm *v.* placebo (40% *v.* 44%; $P<0·77$; children)
Niv *et al.*[56]	54	*L. reuteri* ATCC 55730; 10^{8}	26	Failed to show benefit in GSS over placebo
O'Mahony *et al.*[37]	77	*B. infantis 35624*; 10^{10} *L. salivarius UCC4331*	8	*B. infantis* showed significant improvement in GSS over placebo ($P<0·05$); *L. salivarius* failed to show benefit
Tsuchiya *et al.*[80]	68	*L. helviticus, L. acidophilus, Bifidobacterium*; 10^{9}	12	Global assessment; 80% *v.* 10% ($P<0·01$)
Kim *et al.*[78]	25*	VSL#3; 10^{11}	8	No difference in transit or GSS, reduction in bloating ($P<0·046$)
Sen *et al.*[57]	12	*L. plantarum* 299V; 10^{7}	4	Failed to show reduction in GSS over placebo
Niedzielin *et al.*[55]	40	*L. plantarum* 299V; 10^{7}	4	PEP defined as resolution of pain; 100% *v.* 55% ($P<0·001$)
Nobaek *et al.*[62]	60	*L. plantarum* 299V; 10^{10}	4	Improved flatulence only ($P<0·05$)
Enck *et al.*[59]	298	*E. coli* DSM17252; 10^{7}–10^{8}	8	Complete remission; 18·4% *v.* 4·7% ($P<0·001$)
Williams *et al.*[79]	52	*L. acidophilus* (NCIMB 30157 and NCIMB 30156), *B. lactis* (NCIMB 30172) *and B. bifidum* (NCIMB 30153); 10^{10}	8	Significant improvement in GSS over placebo ($P<0·02$)
Andriulli *et al.*[58]	267	*L. paracasei* B21060 (10^{10}) + prebiotic *v.* prebiotic alone	12	Failure to show improvement over placebo in GSS
Drouault-Holowacz *et al.*[69]	100	*B. longum* LA 101 (29%), *L. acidophilus* LA 102 (29%), *L. lactis* LA 103 (29%) and *S. thermophilus* LA 104 (13%); 10^{10}	4	Failure to show improvement over placebo in GSS
Sinn *et al.*[67]	40	*L. acidophilus* SDC 2012, 2013; 10^{9}	4	Significant reduction in abdominal pain ($P = 0·011$)
Kajander *et al.*[60]	86	*L. GG, L. rhamnosus LC705, B. breve Bb99, Propionibacterium freudenreichii* spp *shermanii* JS	20	Significant reduction in GSS ($P<0·008$)
Guyonnet *et al.*[70]	274†	*B. animalis* DN 173 010	6	Although significant improvement over baseline, no benefit over placebo
Whorwell *et al.*[61]	362	*B. infantis 35624*; 10^{8}	4	Reduction in pain score (PEP; $P<0·03$) Reduction in GSS ($P<0·01$)
Gawronska *et al.*[63]	37‡	*L. GG*; 10^{9}	4	PEP defined as resolution of pain; 33% *v.* 5·1% ($P<0·04$; children)

L., Lactobacillus; B., Bifidobacterium; B. animalis, Bifidobacteria animalis; B. infantis, Bifidobacteria infantis; E. coli; Escherichia coli; S. thermophilus, Streptococcus thermophilus; NCIMB, National Collection of Industrial, Marine and Food Bacteria collection no.; PEP, primary end point; GSS, global symptom score (patient rating of improvement of symptoms overall post-treatment *v.* pretreatment[42]).

*Diarrhoea-predominant IBS.

†Constipation-predominant IBS.

‡Subgroup analysis of IBS in a larger cohort of functional abdominal pain disorders.

some benefit over placebo, one improving flatulence scores[62] and the other demonstrating reduction in pain[55]. The third trial shows no significant benefit, although it was underpowered[57]. However, these preliminary trials have never been followed up with larger multi-centre studies.

Lactobacillus GG

Lactobacillus GG is a strain of probiotic that has shown efficacy in the treatment of infectious diarrhoea in children[12]. There have been two conflicting trials treating childhood IBS and recurrent abdominal pain with *L. GG*, both of which used resolution of abdominal pain as their primary end point[53,63]. The earlier trial found no significant difference in resolution of pain in the treatment arm over placebo (44% *v.* 40%; $P = 0·77$)[53]. The second, however, found that the primary end point was achieved in significantly higher numbers in the treatment arm than placebo (33% *v.* 5%; $P = 0·04$)[63]. A recent Cochrane review of dietary intervention in functional bowel disorders in children has found insufficient evidence to support its use[64]. It should be noted that *L. GG* is a composite strain in one of the probiotic cocktails that have showed benefit in two larger trials[60,65].

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Lactobacillus reuteri *ATCC 55730*

A single trial of fifty-four patients with IBS using *Lactobacillus reuteri* ATCC 55730 over a period of 6 months has demonstrated an improvement in the GSS from baseline but because of a large placebo effect failed to show any benefit over controls[56].

Lactobacillus paracasei *B21060*

A symbiotic preparation, Flortec® (Bracco spA, Milan, Italy), that contains a combination of prebiotic (xylo-oligosaccharide) and probiotic (*Lactobacillus paracasei* B21060) has been used in a large (*n* 267) multi-centre trial, with Flortec® as the treatment arm and xylo-oligosaccharide alone as the control arm[58]. The improvement in global relief scores was found to be similar in the study and control arms, albeit Flortec® was shown to significantly reduce stool frequency in patients with diarrhoea-predominant IBS compared with controls (1·18 *v.* 0·45; $P<0·05$). A recent placebo-controlled trial of a prebiotic product, trans-galactooligosaccharide, in the treatment of IBS has demonstrated significant reduction in GSS over placebo[66]. Thus, the lack of significant difference compared with controls may be in part related to a beneficial effect of the prebiotic in the control arm.

Lactobacillus acidophilus *SDC 2012*

A small single-centre study of forty patients with IBS randomised to *L. acidophilus* SDC 2012 and 2013 or placebo has shown benefit over placebo[67]. Using any reduction in abdominal pain scores as a primary end-point when comparing *L. acidophilus* to placebo a reduction in pain of 23·8% *v.* 0·2% ($P=0·003$) was reported. However, the study did not use a global symptom-relief score as an end point, and using any reduction in pain as 'a responder' is questionable. It is interesting that there appeared to be no appreciable placebo effect in the trial (conducted in South Korea), in contrast to the majority of trials in IBS.

Bifidobacteria infantis *35624*

B. infantis 35624 is a probiotic that was initially designed as a treatment for ulcerative colitis but ultimately failed to demonstrate benefit in a multi-centre clinical trial[68]. However, in a trial of seventy-seven patients with IBS randomised to *B. infantis*, *Lactobacillus salivarius* or placebo, *B. infantis* (but not *L. salivarius*) was shown to reduce pain, bloating and bowel satisfaction scores in comparison with placebo, as well as composite scores[37]. In addition, as discussed earlier, *B. infantis* but not placebo or *L. salivarius* was found to have a profound anti-inflammatory effect in patients with IBS but not in healthy controls. The benefit of *B. infantis* has been replicated in a large multi-centre dose-finding trial of *B. infantis* in 362 female patients with IBS, randomised to four groups taking doses of 10^6, 10^8 or 10^{10} colony-forming units per d or placebo[61]. The group taking *B. infantis* at 10^8 colony-forming units per d was reported to have scored significantly better than the placebo group in all symptom groups including a global assessment of IBS relief that was the primary end point (62·3 (SE 6·2) *v.* 42·0 (SE 6·4); $P<0·02$). It was later discovered that the bacteria in the formulation containing 10^{10} colony-forming units per d were non-viable, perhaps explaining its lack of efficacy.

Bifidobacteria animalis *DN 173010*

Several well-designed large multi-centre trials of probiotics in IBS have failed to demonstrate benefit, again often in part as a result of a high placebo response[58,69,70]. A French multi-centre trial of *B. animalis* DN 173010 in 274 patients with constipation-predominant IBS in primary care has demonstrated symptomatic relief compared with baseline in its primary end point (improvement in a functional bowel disorder quality-of-life score) but not over placebo[70]. However, subgroup analysis of patients with less than three bowel motions per week (*n* 19) at baseline has shown a significant rise in stool frequency compared with controls ($P<0·001$).

Escherichia coli *DSM 17252*

A primary-care-based placebo-controlled trial of *Escherichia coli* (DSM 17252)[59] has been conducted in 298 patients with IBS diagnosed by a primary-care (not Rome[71] criteria) standard in which response was defined as 'clinical remission' with complete resolution of IBS symptoms[72]. In comparison with placebo the treatment arm was reported to have achieved complete remission in 18·4% *v.* 4·6% ($P<0·0004$) of the patients studied (intention-to-treat analysis). In addition, a 50% drop was found in abdominal pain scores (18·9% *v.* 6·7% in treatment and placebo groups respectively; $P=0·001$). This trial was based on a much earlier trial of *E. coli* (DSM 17252) in combination with *Enterococcus faecalis* (DSM 16440) originally published in 1993[73] and more recently re-analysed[50] by re-defining the clinical end points to give a GSS in accordance with modern guidelines. This re-analysis has demonstrated a significantly better response rate (defined by a drop in GSS by 50%) in the treatment arm than in the placebo arm (68·5% *v.* 37·8%; $P<0·001$[50]; data not included in Table 1). Although both these trials failed to use Rome[71] or Manning[74] definitions in their inclusion criteria, they were otherwise large and well designed. Data from primary care rather than secondary care are particularly useful given the majority of patients with IBS are treated by primary-care physicians.

VSL#3®

The combination probiotic VSL#3® has been used in a number of trials for the treatment of ulcerative colitis[75] and pouchitis[76,77]. However, trials of VSL#3® in IBS, although well designed, have reported mixed results. An initial trial of twenty-five patients with diarrhoea-predominant IBS has used colonic transit (measured by scintography) as the primary end point, with reduction in symptom scores as secondary targets[78]. No significant reduction in GI transit was found for the study group, although there was a symptom score reduction in abdominal bloating. Thus, a second, larger, trial was designed using forty-eight patients with a reduction in abdominal

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bloating as the primary end point and colonic transit and other symptoms as secondary end points[54]. Although only a non-significant reduction in abdominal bloating scores was found in the study group *v*. placebo (31·3 (SE 3·1) *v*. 38·5 (SE 3·1); $P = 0·22$), there was a significant reduction in flatulence scores (29·7 (SE 2·6) *v*. 39·5 (SE 2·6); $P = 0·01$). In addition, in the larger trial VSL#3® was shown to significantly retard colonic transit ($P = 0·05$), although without a corresponding change in stool frequency or form. Thus, there is only weak evidence supporting the use of VSL#3® in IBS at present.

Lactobacillus rhamnosus GG, Lactobacillus rhamnosus *LC705*, Bifidobacterium breve, Propionibacterium freudenreichii *spp* shermanii JS

A multi-species probiotic containing *Lactobacillus rhamnosus GG*, *L. rhamnosus* LC705, *Bifidobacterium breve* and *Propionibacterium freudenreichii* spp *shermanii JS* has been used in two trials from the same group. The first 6-month trial of 103 patients with IBS has found a mean difference in reduction of the total symptom scores (the primary end point) of 7·7 points ($P = 0·015$)[65]. These findings were confirmed by a follow-up study of eighty-six patients, with a difference in reduction in GSS of eleven points ($P<0·01$)[60]. However, marked differences in baseline severity scores were found between treatment groups and controls, with the treatment group having greater symptom severity and therefore more likely to improve. In addition, a high percentage (22) of both control and treatment arms were prescribed antibiotics in the treatment period. A notable feature in these trials was the longer treatment period of 5 and 6 months respectively with a consistent GSS improvement over the treatment course.

LAB4

A study that used *L. acidophilus* (NCIMB 30157 and 30156) in combination with *Bifidobacterium lactis* (NCIMB 30172) and *Bifidobacterium bifidum* (NCIMB 30153) has also demonstrated benefit in IBS[79]. At the end of the 8-week trial of fifty-two patients with IBS randomised to the probiotic combination (LAB4®; Cultech Ltd, Port Talbot, West Glamorgan, UK) or placebo a significant drop in the symptom severity score was found in the study arm compared with the controls (133 *v*. 80; $P<0·05$). However, once again the study arm had a higher baseline severity score than the placebo arm; in addition, the benefit was no longer significant 2 weeks after stopping the probiotic.

Discussion

Although understanding of the GI tract continues to expand, IBS remains a difficult condition to treat. The key to this difficulty is in part the heterogeneous nature of the syndrome. Although the clinical symptoms of altered bowel habit, pain and bloating are frequently similar in different classes of IBS, the underlying aetiologies can be diverse. Clinicians need a range of therapeutic options that reflect this heterogeneity, whether they be neuromotility agents, psychosocial therapy, dietary advice or microbial manipulation with probiotics.

Following the evidence summarised earlier, the probiotics with the greatest efficacy data in treating IBS are *B. infantis* 35624 and *E. coli* DSM 17252. Both these probiotics have had initial successful trials supported by larger multi-centre studies[37,50,59,61]. *B. infantis* has *in vitro* and human data supporting a putative mechanism of action. Unfortunately, the second randomised controlled trial of *B. infantis* was only conducted in women[61] and therefore there is little evidence to support its use in men. Although this trial was conducted in all subgroups of IBS, further analysis suggests that *B. infantis* is most effective in patients with diarrhoea-predominant IBS (reduction in composite symptom score compared with placebo; −0·99, $P = 0·027$) and there is no benefit in patients with IBS with alternating stool pattern (−0·15, $P = 0·84$). In the constipation-predominant IBS group, although the difference in the composite score compared with placebo is not significant (−1·32, $P = 0·074$), this outcome is probably the result of a reduced sample size.

The Finnish probiotic combination of *L. rhamnosus GG, L. rhamnosus* LC705*, B. breve, Propionibacterium freudenreichii* spp s*hermanii JS* has also demonstrated benefit in two sequential trials[60,65]. However, both trials recruited from a single centre and were conducted by the same investigators. A larger, ideally multi-national, trial would be helpful before making stronger recommendations. Many other products have been hampered by a large placebo effect; in particular, a large trial of *B. animalis* DN 173010[70]. However, given the subgroup analysis showing benefit in patients with a stool frequency of less than three per week, the use of *B. animalis* DN 173010 could be cautiously recommended in patients with severe constipation-predominant IBS, although clearly further data are needed. There are obviously a number of smaller trials that have demonstrated benefit[67,79,80], but given the limited numbers and lack of supporting evidence it is difficult to recommend their use at this stage. Single-centre pilot data suggesting benefit for a probiotic agent in treating IBS should be supported by data from larger multi-centre trials.

There have been a number of meta-analyses on probiotics in IBS recently, all of which agree that probiotics are beneficial to varying extents. One meta-analysis has shown a relative risk of not improving the GSS of 0·77 (95% CI 0·62, 0·94)[47], another meta-analysis has reported a relative risk of not improving the GSS of 0·72 (95% CI 0·57, 0·88)[45] and another meta-analysis has found an OR of symptomatic improvement of 1·63 (95% CI 1·23, 2·17)[48]. However, meta-analyses or systematic reviews that group disparate species of probiotics together always risk diluting evidence of successful trials with studies using entirely different species and vice versa.

Like most therapies in IBS probiotics are unlikely to be beneficial for all patients. However, given their impressive safety profile and their relative low cost, a trial of a probiotic agent is certainly worth considering. Given the wide availability of products to the public, patients need careful guidance as to which product is likely to be of benefit in order not to be frustrated. Care must be taken to recommend the exact strain or species that has shown benefit in

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treating IBS, and not to extrapolate success of one probiotic species to another. In addition, further research is needed to predict which patient groups are most likely to respond to probiotics, perhaps through faecal microbial profiling. The understanding of the GI microbiota and its interaction with the host is in its infancy; however, its manipulation offers therapeutic benefit in a number of GI disorders including IBS.

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