

# Do probiotics improve symptoms in patients with irritable bowel syndrome?

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**Abstract:** There is increasing evidence that inflammation or a disturbance of the flora within the gut might contribute to the pathogenesis of irritable bowel syndrome (IBS), at least in a proportion of cases. As a consequence it has been speculated that, as some probiotic bacteria have a range of anti-inflammatory and immunomodulatory properties, the administration of such organisms might prove to be beneficial in this condition. It has to be acknowledged that the quality and design of trials of probiotics in IBS has been somewhat variable but the majority have shown benefit, although some bacteria appear to be more effective than others. More recent studies using *Bifidobacterium infantis* 35624 and *Bifidobacterium lactis* DN-173-010 have given particularly encouraging results. Issues for the future include determining which organisms are most effective, defining optimal doses, comparing methods of delivery and assessing the role of mixtures or the addition of prebiotics.

**Keywords:** irritable bowel syndrome, probiotics, bifidobacteria

## Rationale for probiotics in irritable bowel syndrome

As long ago as 1962, it was recognised that some cases of irritable bowel syndrome (IBS) appeared to follow an acute gastrointestinal infection [Chaudhary and Truelove, 1962]. This concept of postinfectious IBS has been confirmed in a number of subsequent studies with between 4% and 31% of patients with IBS dating their symptoms from an infective episode [Marshall *et al.* 2006; Rodriguez and Ruigomez, 1999; Neal *et al.* 1997; McKendrick and Read, 1994]. The mechanism by which infection could lead to continuing symptoms is not fully understood but it has been suggested that it might be due to persisting inflammation [Spiller, 2004a, 2004b]. Evidence in favour of this hypothesis has emerged from a number of histological studies of the mucosa in patients with IBS [Barbara *et al.* 2004; Chadwick *et al.* 2002; Spiller *et al.* 2000; Gwee *et al.* 1999] although in one there was also inflammation in patients who denied any antecedent enteric infection [Chadwick *et al.* 2002]. Another situation which seems to predispose to IBS is the previous use of antibiotics [Maxwell *et al.* 2002; Mendall and

Kumar, 1998], particularly if they are used on a long-term basis such as in patients with acne or chronic sinus infection. This might result in a change in the bacterial flora of the gut and studies both using culture or molecular techniques suggest that there might be subtle differences in patients with IBS compared with healthy controls [Kassinen *et al.* 2007; Matto *et al.* 2005; Malinen *et al.* 2005; Si *et al.* 2004]. It has also been reported that small bowel bacterial overgrowth may be important in some patients with IBS although this particular topic remains somewhat controversial [Bratten *et al.* 2008; Majewski and McCallum, 2007; Posserud *et al.* 2007; Pimentel *et al.* 2003b, 2000]. However, it is possible that at least a proportion of patients might suffer from this problem. In contrast to the observation that IBS can follow the use of antibiotics, there is now some evidence that the administration of a nonabsorbable antibiotic can actually lead to symptom reduction [Pimentel *et al.* 2006; Sharara *et al.* 2006]. All these data indicate that inflammation or imbalance of the bacterial flora of the gut might play a part in the pathogenesis of IBS. It is against this background that the possibility that probiotics

*Ther Adv Gastroenterol*  
(2009) 2(Suppl 1) S37–S44  
DOI: 10.1177/  
1756283X09335637  
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might have a beneficial effect in IBS has been entertained. Probiotics have been shown to have a whole range of beneficial effects which are listed in Box 1. The most commonly used probiotic organisms are the lactobacillae and bifidobacteria and it is important to note that different organisms can have completely different activity so that, for instance, one type of bifidobacterium may not exhibit the same properties as another.

### Probiotics in IBS

Table 1 [Guyonnet *et al.* 2007; Gawronska *et al.* 2007; Niv *et al.* 2005; Bausserman and Michail, 2005; Sen *et al.* 2002; Niedzielin *et al.* 2001; Nobaek *et al.* 2000; O'Sullivan and O'Morain, 2000; Halpern *et al.* 1996; Gade and Thorn, 1989] lists the results of controlled clinical trials that have been undertaken using single probiotic preparations. Table 2 [Drouault-Holowacz *et al.* 2008; Enck *et al.* 2008; Kajander *et al.* 2008, 2005;

#### Box 1. Some properties of probiotics.

Enhance host's anti-inflammatory and immune response  
 Stimulate anti-inflammatory cytokines  
 Improve epithelial cell barrier  
 Exhibit epithelial adhesion  
 Inhibit bacterial translocation  
 Inhibit growth of pathogens (e.g. salmonella)  
 Inhibit adhesion of viruses (e.g. rotavirus)  
 Reduce hypermotility (animal model)  
 Reduce visceral hypersensitivity (animal model)  
 Inactivate bile acids  
 Elaborate active proteins and metabolites with following characteristics:  
 immune modulatory activity  
 proteolytic/bacteriocidal activity  
 toxin binding activity.

**Table 1.** Controlled clinical trials of single probiotic preparations in irritable bowel syndrome.

Organism	<i>n</i>	Outcome	Reference
<i>L. plantarum</i>	60	↓ pain, flatulence	Nobaek <i>et al.</i> (2000)
<i>L. plantarum</i>	20	↓ pain	Niedzielin <i>et al.</i> (2001)
<i>L. plantarum</i>	12	negative	Sen <i>et al.</i> (2002)
<i>L. GG</i>	25	negative	O'Sullivan and O'Morain (2000)
<i>L. GG</i>	50	↓ bloating	Bausserman and Michail (2005)
<i>L. GG</i>	104	↓ pain	Gawronska <i>et al.</i> (2007)
<i>L. reuterii</i>	54	negative	Niv <i>et al.</i> (2005)
<i>L. acidophilus</i>	18	↓ global score	Halpern <i>et al.</i> (1996)
<i>S. faecium</i>	54	↓ global score	Gade <i>et al.</i> (1989)
<i>B. lactis</i>	274	↓ digestive symptoms	Guyonnet <i>et al.</i> (2007)

B., Bifidobacterium; L., Lactobacillus; *n*, number of patients; S., Streptococcus.

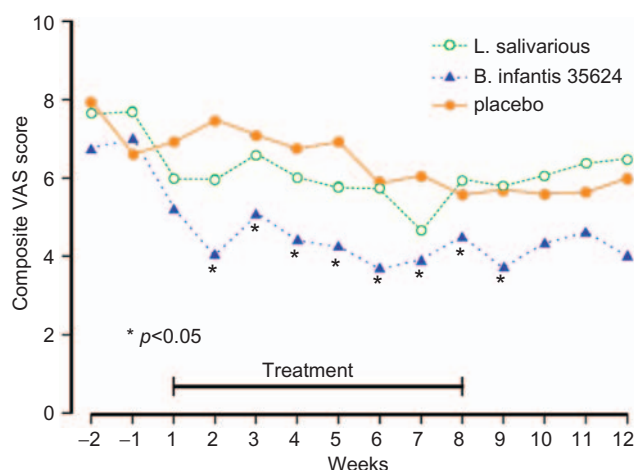
**Table 2.** Controlled clinical trials of probiotic mixtures in irritable bowel syndrome.

Organism	<i>n</i>	Outcome	Reference
VSL#3 (× 8)	25	↓ bloating	Kim <i>et al.</i> (2003)
VSL#3 (× 8)	48	↓ flatulence	Kim <i>et al.</i> (2005)
Mixture (× 4)	103	↓ global score	Kajander <i>et al.</i> (2005)
Mixture (× 4)	86	↓ global score	Kajander <i>et al.</i> (2008)
Mixture (× 4)	52	↓ global score	Williams <i>et al.</i> (2008)
Mixture (× 4)	106	negative	Drouault-Holowacz <i>et al.</i> (2008)
Mixture (× 2)	40	↓ pain	Kim <i>et al.</i> (2006)
Mixture (× 2)	40	↓ pain	Sinn <i>et al.</i> (2008)
Mixture (× 2)	297	↓ global score	Enck <i>et al.</i> (2008)

*n*, number of patients.

**Table 3.** Composition of probiotic mixtures from Table 2.

× 8	3 bifidobacteria, 4 lactobacillae, 1 streptococcus
× 4	2 lactobacillae, 1 bifidobacterium, 1 propionibacterium
× 4	2 lactobacillae, 2 bifidobacterium
× 4	2 lactobacillae, 1 bifidobacterium, 1 streptococcus
× 2	1 <i>B. subtilis</i> , 1 streptococcus
× 2	2 lactobacillae
× 2	1 enterococcus, 1 <i>E.coli</i> (cell fragments)

**Figure 1.** Effect of *Bifidobacterium infantis* 35624, *Lactobacillus salivarius* or placebo on composite score in irritable bowel syndrome.

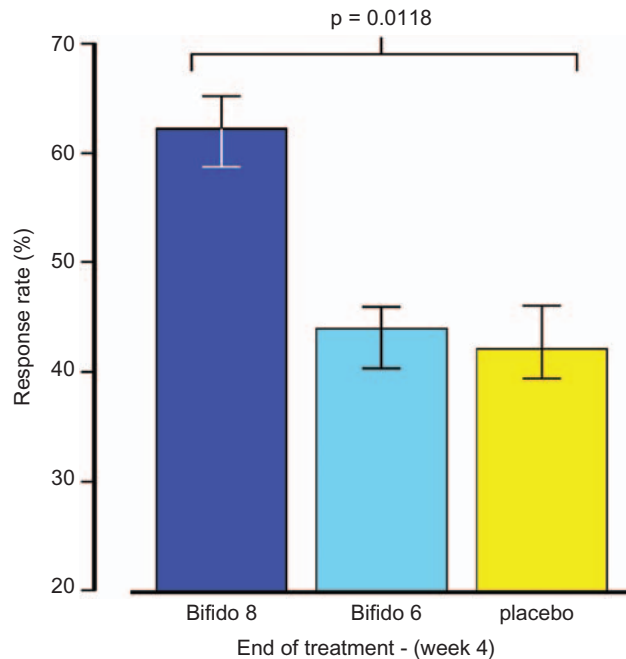
Sinn *et al.* 2008; Williams *et al.* 2008; Y.G. Kim *et al.* 2006; H.J. Kim 2005, 2003] documents studies using mixtures of organisms, while Table 3 shows the composition of these various mixtures. Unfortunately, there is considerable variation in trial design and outcome measures but it is clear that different symptoms are improved depending on the preparation used and that some products appear to be more effective than others. However, the results are generally positive with 15 of the 19 studies listed showing at least some effect.

### Specific studies of probiotics in IBS

Recently, the group based at the University of Cork isolated a bifidobacterium (*B. infantis* 35624) which they considered to have promise in IBS. In 2005 they reported a study comparing this organism at a strength of  $1 \times 10^{10}$  cells in 100 ml of malted milk per day with *Lactobacillus salivarius*, at a similar concentration, in a similar volume of malted milk per day or 100 ml of malted milk placebo [O'Mahony *et al.* 2005]. Twenty-five patients were recruited to each group and studied for 8 weeks. Figure 1

compares the results for the three groups in terms of a composite IBS symptom score. As can be seen, there was a significant advantage for the bifidobacterium compared with the other two groups and the beneficial effect appeared to last after treatment was discontinued. The authors also studied the effect of treatment on the ratio of an anti-inflammatory cytokine (IL-10) to a proinflammatory cytokine (IL-12). This ratio appeared to be in a proinflammatory state before treatment and this became normalised after administration of the bifidobacterium. Thus, this particular probiotic appears to have promising effects in IBS but a milk delivery system is obviously cumbersome and it would be far better if this could be given in a capsule. As a consequence, a dose-ranging study was undertaken of *B. infantis* 35624 in capsule form [Whorwell *et al.* 2006].

Three-hundred-and-sixty-two female patients with uncomplicated IBS, irrespective of whether they had diarrhoea or constipation, were randomly allocated to take one of four possible treatments for 4 weeks. These were one capsule containing either *B. infantis* 35624,  $1 \times 10^{10}$ ,



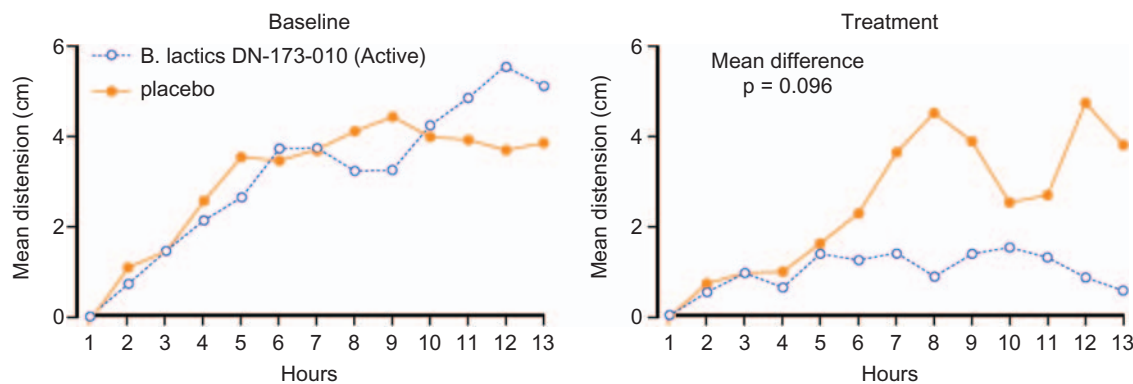
**Figure 2.** Comparison of the effect of placebo or *Bifidobacterium infantis* 35624 at a dose of  $1 \times 10^8$  (Bifido 8) or  $1 \times 10^6$  (Bifido 6) colony forming units on global outcome in irritable bowel syndrome.

$1 \times 10^8$  or  $1 \times 10^6$  colony forming units per capsule, or matching placebo. At the end of the study it became apparent that the  $10^{10}$  dose of the probiotic, which was the dose used in the original milk-based study, was ineffective. Further investigation of this problem revealed that the contents of the capsule failed to disperse because the organism secreted an intensely hygroscopic exopolysaccharide coating rendering the preparation inactive. Analysis of the data for the other three groups revealed that the  $1 \times 10^8$  preparation was significantly superior to either the  $1 \times 10^6$  or placebo. This was seen for all symptoms of IBS and in terms of global outcome, the response rate was over 20% greater than that observed for placebo (Figure 2). In addition to confirming the previous positive results for this probiotic, this study emphasised the slow onset of action of these agents suggesting that short-term studies in this field might fail to detect an effect. Furthermore, bioavailability is obviously another critical consideration as the failure of the  $1 \times 10^{10}$  dose was totally unexpected.

#### Possible effects of probiotics in bloating and distension

The term 'bloating' is usually used to describe the sensation of an increase in abdominal girth, whereas 'distension' should only be used when

this feeling is accompanied by an actual increase in girth. Both these features are extremely common aspects of IBS, are particularly difficult to treat and often rated as the patient's most intrusive symptom. In order to further understand this phenomenon, the technique of abdominal inductance plethysmography (AIP) has been developed [Reilly *et al.* 2002; Lewis *et al.* 2001]. This is based on the principle that a loop of wire has a certain inductance which changes according to the shape of the loop. Therefore, if a wire is stitched into an elasticated belt and placed around the abdomen, any change in girth is detected as a change in inductance and after appropriate manipulation can be subsequently displayed as a measurement. The belt is unobtrusive, can be worn for up to 24 hours and is accurate down to 1 mm. Using this technique, it has been shown that 50% of patients who report bloating also exhibit distension and girth can increase by as much as 12 cm during the course of the day [Houghton *et al.* 2006]. Distension is more common in patients with constipation [Houghton *et al.* 2006] and is also associated with delayed transit [Agrawal *et al.* 2006]. Consequently, either relieving constipation or accelerating transit should theoretically lead to an improvement in distension. *Bifidobacterium lactis* DN-173-010 has previously been shown to accelerate transit [Marteau *et al.* 2002] and



**Figure 3.** Recording of abdominal distension over 12 hours before and after treatment with either *Bifidobacterium lactis* DN-173-010 (Activia®) or placebo.

reduce the subjective symptom of bloating [Guyonnet *et al.* 2007] and, therefore, might potentially relieve distension which can be measured objectively using AIP. In addition increased methane production from gut bacteria has been associated with constipation in IBS [Pimentel *et al.* 2003a, 2003c] raising the possibility that alteration of gut flora, perhaps by the use of probiotics, may help to relieve this problem although this has not been assessed for *B. lactis* DN-173-010.

Thirty-four patients with constipation predominant IBS were randomised to receive either *B. lactis* DN-173-010 ( $1.25 \times 10^{10}$  colony forming units) in the form of Activia® 125 g twice daily or matching placebo [Agrawal *et al.* 2008]. Both active and control products were without flavour and had a similar appearance, texture and taste. Distension was measured using AIP at baseline and again after 4 weeks treatment. In addition, small bowel transit was assessed using a test meal and large bowel transit using a radio-opaque marker technique. Symptoms were also recorded. Active treatment resulted in a significant acceleration of small bowel as well as large bowel transit and this was accompanied by a 78% reduction in maximum distension which was significantly greater than the 29% reduction in those receiving the control product. Figure 3 shows the 12 hour AIP data for active and control products during the baseline and treatment phases. With respect to symptoms, abdominal pain and overall IBS score were significantly improved despite the fact that the study was not powered to detect symptom change. Therefore, in addition to supporting the role of this probiotic in improving distension in IBS, this study strengthens the

notion that accelerating gastrointestinal transit does reduce this troublesome symptom.

### Conclusion

There seems little doubt that probiotics have some beneficial effects in some patients with IBS. However, they are unlikely to be as potent as pharmacological agents and, therefore, will probably have the greatest utility in patients at the milder end of the spectrum of disease severity. It is important to remember that not all probiotics are the same and that they differ in their activity in relation to IBS. Another critical factor is formulation and bioavailability and we need to know whether the products that are being sold to the general public actually have enough viable organisms to make a difference, especially as large doses are required to have a therapeutic effect. A further question that needs resolving is whether mixtures of probiotics are necessarily always a good approach, as there is at least hypothetically, the possibility that some organisms might actually inhibit the activity of others.

IBS is a condition that many patients suffer from over a lifetime and, therefore, the safety of anything they are taking for their condition is of considerable importance. Consequently, the concept of taking a preparation that has perceived benefits on the gut microflora without doing any harm has high patient acceptability.

The National Institute for Health and Clinical Excellence (NICE) in the UK has recently reviewed the treatment of IBS and has made the following recommendation about the use of probiotics [NICE 2008]:



Probiotics do not appear to be harmful (unless they come from an unreliable source) and they might benefit people with IBS. They should be advised to take the product for at least four weeks while monitoring the effect.

### Conflict of interest statement

Professor Whorwell has received research funding from Danone, Paris, France and Procter and Gamble, Cincinnati, USA.

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