**Systematic review of randomised controlled trials: Probiotics for functional constipation**

Anna Chmielewska, Hania Szajewska

**Abstract**

**AIM:** To systematically evaluate and update evidence on the efficacy and safety of probiotic supplementation for the treatment of constipation.

**METHODS:** The MEDLINE, EMBASE, CINAHL, and Cochrane Library databases were searched in May 2009 for randomised controlled trials (RCTs) performed in paediatric or adult populations related to the study aim.

**RESULTS:** We included five RCTs with a total of 377 subjects (194 in the experimental group and 183 in the control group). The participants were adults (three RCTs, n = 266) and children (two RCTs, n = 111) with constipation. In adults, data suggests a favourable effect of treatment with *Bifidobacterium lactis* DN-173 010, *Lactobacillus casei* Shirota, and *Escherichia coli* Nissle 1917 on defecation frequency and stool consistency. In children, *L. casei rhamnosus Lcr35*, but not *L. rhamnosus GG*, showed a beneficial effect.

**CONCLUSION:** Until more data are available, we believe the use of probiotics for the treatment of constipation condition should be considered investigational.

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**Key words:** Randomised controlled trials; Constipation; Probiotics; Adults; Children

**Peer reviewer:** Kristin A Verbeke, Professor, Pathophysiology, Section of Gastroenterology, Katholieke Universiteit Leuven, Herestraat 49, Leuven 3000, Belgium


**INTRODUCTION**

Constipation is a common condition affecting children and adults[3,4]. In the vast majority of cases, no underlying organic cause is found and functional constipation is diagnosed[5,6]. The standard treatment consists of disimpaction and the administration of laxatives to achieve a normal bowel habit of passing a soft stool without pain. Even though traditional treatment is well established and safe, for many patients it does not provide satisfying improvement, prompting interest in other therapeutic strategies[7].

Currently, probiotics, defined as live microorganisms which when administered in adequate amounts confer a health benefit on the host[8], are increasingly being used in the management of constipation. Those most widely studied are organisms within the genera *Bifidobacterium*...
and Lactobacillus. There are several reasons why probiotics might have therapeutic potential for the treatment of constipation. Firstly, there are data demonstrating differences in the intestinal microbiota between healthy individuals and patients with chronic constipation. The key features are an increased number of clostridia and bifidobacteria, with different species of clostridia and enterobacteriaceae being frequently isolated. A number of key questions remain to be answered, principally, what is the origin of this dysbiosis? Is dysbiosis a secondary manifestation of constipation, or is it a factor contributing to constipation? Secondly, studies involving the administration of B. lactis DN-173 010 have shown improved colonic transit times, both in a healthy population and in constipated patients. Finally, probiotics lower the pH in the colon. This reduction in pH is due to the bacterial production of short-chain fatty acids (butyric acid, propionic acid, and lactic acid). A lower pH enhances peristalsis in the colon and, subsequently, might decrease the colonic transit time.

In view of the uncertainty regarding the use of probiotics for the treatment of constipation, we decided to systematically review and update data from randomised controlled trials (RCTs) on the efficacy and safety of using probiotics for the treatment of constipation in both paediatric and adult populations. If the probiotics were effective, another aim was to determine what strain(s) of probiotic microorganisms is the most effective.

MATERIALS AND METHODS

The guidelines from the Cochrane Collaboration for undertaking and reporting the results of this systematic review were followed. Briefly, we searched three electronic bibliographic databases (MEDLINE, EMBASE, and CINAHL) and the Cochrane Library. Every database was searched from inception to May 2009. Additionally, the reference lists from identified studies and key review articles assessing the effects of probiotics on the treatment of constipation were searched. While no language restrictions were applied, in practice the search was restricted to English-language papers, papers written in languages known to the reviewers, or those with English-language abstracts. The review was restricted to RCTs only carried out in paediatric or adult populations. Participants in the experimental groups received probiotics for the treatment of constipation, or is it a factor contributing to constipation? Secondly, studies involving the administration of B. lactis DN-173 010 have shown improved colonic transit times, both in a healthy population and in constipated patients. Finally, probiotics lower the pH in the colon. This reduction in pH is due to the bacterial production of short-chain fatty acids (butyric acid, propionic acid, and lactic acid). A lower pH enhances peristalsis in the colon and, subsequently, might decrease the colonic transit time.

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Table 1  Characteristics of included trials

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Probiotic</th>
<th>Design</th>
<th>Allocation concealment/Blinding/Intention-to-treat analysis/Description of withdrawals or dropouts</th>
<th>Exp/cont (age, yr)</th>
<th>Definition of constipation</th>
<th>Duration of intervention (daily dose)</th>
<th>Placebo</th>
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<tbody>
<tr>
<td>Studies in adults</td>
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<tr>
<td>Mollenbrink et al. 1994 (Germany)</td>
<td><em>E. coli Nissle</em> 1917</td>
<td>RCT, crossover</td>
<td>Unclear/Yes/No/Yes</td>
<td>35/35 (18-60)</td>
<td>&lt; 2 BM per week</td>
<td>4 + 4 wk</td>
<td>25 × 10⁶ CFU  Placebo</td>
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<tr>
<td>Koebnick et al. 2003 (Germany)</td>
<td><em>L. casei Shirotta</em></td>
<td>RCT, parallel</td>
<td>Unclear/Yes/Yes/Yes</td>
<td>35/35 (18-70)</td>
<td>Not provided</td>
<td>4 wk</td>
<td>6.5 × 10⁶ CFU, probiotic beverage  Placebo</td>
</tr>
<tr>
<td>Yang et al. 2008 (China)</td>
<td><em>B. lactis</em> DN-173 010</td>
<td>RCT, parallel</td>
<td>Unclear/No/Yes/Yes</td>
<td>63/63 (25-65, only women)</td>
<td>&lt; 3 BM per week; increased stool hardness; non-organic constipation and habitual constipation</td>
<td>2 wk</td>
<td>Fermented milk containing 1.25 × 10⁹ CFU of probiotic plus yoghurt strains Placebo</td>
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<tr>
<td>Studies in children</td>
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<tr>
<td>Banaszekiewicz et al. 2005 (Poland)</td>
<td><em>L. rhamnosus</em> GG</td>
<td>RCT, parallel (computer-generated randomisation list)</td>
<td>Yes/Yes/Yes/Yes</td>
<td>43/41 (2-16)</td>
<td>&lt; 3 BM per week during 14 days for at least 12 wk</td>
<td>12 wk</td>
<td>Lactulose plus LGG 2 × 10⁹ CFU Lactulose plus placebo</td>
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<tr>
<td>Bu et al. 2007 (Taiwan)</td>
<td><em>L. casei rhamnosus</em> Lcr35</td>
<td>RCT, parallel (computer-generated randomisation list)</td>
<td>Yes/Yes/Yes/Yes</td>
<td>18/9 (&lt; 10)</td>
<td>&lt; 3 BM per week for &gt; 2 mo plus at least one of the criteria: anal fissures with bleeding due to constipation, faecal soiling, or passage of large and hard stool</td>
<td>4 wk</td>
<td>8 × 10⁹ CFU Placebo (starch)</td>
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</table>

RCT: Randomised controlled trials; CFU: Colony-forming units; BM: Bowel movements.

Four of the included studies were RCTs with a parallel design, and the remaining included RCT had a crossover design. All were placebo-controlled trials. The participants were adults (three RCTs, n = 266) and children (two RCTs, n = 111) with constipation defined as stated in Table 2. The following different probiotic strains were tested: *Bifidobacterium lactis* DN-173010, *E. coli Nissle* 1917, *Lactobacillus casei rhamnosus* Lcr35, *L. casei* Shirotta, and *L. rhamnosus* GG. One RCT assessed the effectiveness of using *L. rhamnosus* GG as an adjunct to lactulose therapy compared with treatment with lactulose alone, which involves the duration of the interventions in the parallel-design studies were two weeks in one study, four weeks in two studies, and 12 wk in one study. The duration of the intervention in the crossover design study was eight weeks. The doses of the probiotic used ranged from 8 × 10⁶ to 25 × 10⁹ colony-forming units (CFU)/d.

The methodological quality of the trials varied. While all were randomised trials, the randomisation method was described and adequate in only two RCTs. Except for one study, double blinding was applied in the remaining RCTs. An adequate description of the intention-to-treat analysis was provided in all but one study. The withdrawals and dropouts were described adequately in all of the studies, and all included an adequate number (i.e. ≥ 80%) of participants in the final analysis.

**Study description**

**RCTs in adults:** The study by Mollenbrink and Bruckschen was a single-centre, randomised, double-blind, crossover trial that investigated the efficacy of treating 70 constipated patients with *E. coli Nissle* 1917 or placebo. After four weeks of treatment, there was a significant difference in the mean number of stools per week in the *E. coli* group compared with the placebo group (4.9 ± 1.5 vs 2.6 ± 1.0, respectively, MD 2.3 stools per week, 95% CI 1.7 to 2.9), which also remained significant at eight weeks (6 ± 1.3 vs 1.9 ± 1.5, respectively, MD 4.1, 95% CI 3.2 to 5). This study also revealed a significant difference between the probiotic and the control group in the incidence of hard stools (2/34 vs 16/30, respectively, RR 0.1, 95% CI 0.03 to 0.4). Both the effectiveness and tolerance of the treatment, as assessed both by a physician and the patients, were significantly better in...
that in the *E. coli* group. The authors concluded that *E. coli* Nissle 1917 is successful in the therapy of idiopathic chronic constipation.

The study by Koebnick *et al* [12] was a single-centre, double-blind, placebo-controlled, randomised trial involving 70 patients with symptoms of chronic constipation. All of the patients received either a probiotic beverage containing *L. casei* Shirota or placebo for four weeks. Patients completed a questionnaire related to their gastrointestinal symptoms, well-being, and stool habits, and underwent a medical examination weekly. The severity of constipation, flatulence, and bloating was divided into four categories (severe, moderately severe, mild, and no symptoms). Compared to the placebo group, those randomised to the *L. casei* Shirota group experienced a significant improvement in the self-reported severity of constipation and stool consistency. That is, they experienced significant reductions in the occurrence of moderate and severe constipation (*P* < 0.001), the degree of constipation (*P* = 0.003), and the occurrence of hard stools (*P* < 0.001), and increased their defecation frequency (*P* = 0.004). However, the occurrence and degree of flatulence or bloating sensation did not significantly differ between the groups.

In the most recent study, Yang *et al* [14] administered a fermented milk product containing *B. lactis* DN-173 010 and some yoghurt strains (*S. thermophilus* (1.2 × 10^9 CFU/pot 100 g) (experimental group) or an acidified milk containing non-living bacteria but no *B. lactis* DN-173 010 or yoghurt strains (control group) for two weeks to constipated women. Comparison of the experi-

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<td>Stool consistency scores [week 1: 1.1 ± 0.9 vs 1.6 ± 1.1, MD -0.5 (95% CI -0.85 to -0.18); week 2: 0.8 ± 1.0 vs 1.6 ± 1.1; MD -0.8 (95% CI -1.14 to -0.44)]</td>
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<td>Banaszkiewicz <em>et al</em> 2005 (Poland) L. rhamnosus GG</td>
<td>Treatment success (≥ 3 spontaneous BMs per week with no episodes of faecal soiling) (NS)</td>
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<tr>
<td>Bu <em>et al</em> 2007 (Taiwan) L. casei rhamnosus Lc35</td>
<td>Treatment success (≥ 3 spontaneous BMs per week with no episodes of faecal soiling in the fourth week) (14/18 vs 1/9, RR 7, 95% CI 1.1 to 45; <em>P</em> = 0.01)</td>
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1Mean values are presented for the experimental group and control group, respectively; 2 Comparisons of experimental and control group. NS: Not significant.
mental group with the control group revealed a significantly higher stool frequency after one week of product administration (3.5 ± 1.5 vs 2.5 ± 0.9, respectively, MD 1.0 stool per week, 95% CI 0.6 to 1.4) and at two weeks (4.1 ± 1.7 vs 2.6 ± 1.0, respectively, MD 1.5 stool per week, 95% CI 0.7 to 1.6). The extent of defecation difficulty was assessed as 0-3 point defecation condition scores. In brief, 0 points indicates normal defecation, while 3 points indicates often abdominal pain or anal burning sensation to influence defecation. (Table 2 for complete categorisation of defecation condition scores). Both at one and two weeks after product consumption, there was a significant improvement in the defecation condition scores in the experimental group compared with the control group: 1.1 ± 0.9 vs 1.6 ± 1.1, respectively (MD -0.5, 95% CI -0.85 to -0.18) at 1 wk and 0.8 ± 1.0 vs 1.6 ± 1.1, respectively (MD -0.79, 95% CI -1.14 to -0.44) at 2 wk. The stool consistency score was determined according to the Bristol Stool Scale. In brief, 0 points indicates stools like a sausage or a snake, smooth and soft, while 2 points indicates separating hard lumps, like fruit kernel (difficult discharge) (Table 2). The stool consistency scores were significantly improved in the B. lactis DN-173010 group compared to the control group at 1 wk (1.0 ± 0.8 vs 1.4 ± 1.0, respectively, MD -0.4, 95% CI -0.73 to -0.12) and at 2 wk (0.6 ± 0.8 vs 1.3 ± 1.0, respectively, MD -0.7, 95% CI -1 to -0.4). There were no significant differences between groups in food intake and safety parameters. The researchers concluded that the administration of a fermented milk product containing B. lactis DN-173010 has a beneficial effect on stool frequency, defecation conditions, and stool consistency in adult women with constipation.

RCTs in children: Only two RCTs have addressed the use of probiotics in the treatment of constipation in children. In the study by Banaszkiewicz and Szajewska[31], 84 children (aged: 2-16 years) with constipation (≤ 3 spontaneous bowel movements per week for at least 12 wk) were enrolled in a double-blind, randomised, placebo-controlled trial in which they received 1 mL/kg per day of 70% lactulose plus 10⁹ CFU of L. rhamnosus GG (experimental group, n = 43) or a lactulose-containing placebo (control group, n = 41) orally twice daily for 12 wk. The primary outcome measure was treatment success; all analyses were performed on an intention-to-treat basis. Treatment success was defined as ≥ 3 spontaneous bowel movements per week with no episodes of faecal soiling. Treatment success was similar in the control and experimental groups at 12 wk [28/41 (68%) vs 31/43 (72%), respectively; P = 0.7] and at 24 wk [27/41 (65%) vs 27/43 (64%), respectively; P = 1.0]. The groups also did not differ in their mean number of spontaneous bowel movements per week or episodes of faecal soiling per week at four, eight, and 12 wk. Adverse events and overall tolerance did not differ between groups. It was concluded that L. rhamnosus GG, as dosed in this study, was not an effective adjunct to lactulose in treating constipation in children.

The study by Bu et al[30] evaluated the effect of treating children with chronic constipation with L. casei rhamnosus Lcr35 compared to magnesium oxide (MgO) or placebo; however, only the latter comparison is valid for this systematic review. For those treated with the probiotic (n = 18) compared with placebo (n = 9), the trial showed an increase in the treatment success defined as ≥ 3 spontaneous defecations per week with no episodes of faecal soiling (14/18 vs 1/9, respectively, RR 7, 95% CI 1.1 to 45), an increase in the faecal defecation frequency (times/d) (0.57 ± 0.17 vs 0.37 ± 0.10, respectively, MD 0.2, 95% CI 0.1 to 0.3), a reduction in abdominal pain (frequency) (1.9 ± 1.6 vs 6.7 ± 3.3, respectively, MD -4.8, 95% CI -6.6 to -3), a reduction in the use of glycerin enemas during the four weeks of therapy (frequency) (1.6 ± 1.9 vs 4.0 ± 2.1, respectively, MD -2.4, 95% CI -4 to -0.8), and a decrease in the percentage of hard stools in the total number of defecations (22.4 ± 14.7 vs 75.5 ± 6.1, respectively, MD -53%, 95% CI -63 to -43). However, there was no difference between groups in the use of lactulose or the number of episodes of faecal soiling. No change in appetite was observed. However, the sample size was too small to draw any meaningful conclusion.

**Adverse events**

The probiotics were well tolerated, and no adverse events associated with this supplementation were reported in any of the trials.

**DISCUSSION**

**Principal findings**

The objective of this review was to provide some resolution to the uncertainty regarding the use of probiotics for the treatment of functional constipation in paediatric and adult populations. The main finding of the review is that there is very limited evidence available from controlled trials to evaluate with certainty the effect of probiotic administration on constipation. Data published to date suggest that adults with constipation might benefit from ingestion of B. lactis DN-173010, L. casei Shirota, and E. coli Nissle 1917, which were shown to increase defecation frequency and improve stool consistency. However, in some cases, even if there was a significant difference in results, their clinical relevance is unclear. For example, compared with placebo, B. lactis DN-173010 increased only by one the number of stools per week. In children, the administration of L. rhamnosus GG was not effective, while the administration of L. casei rhamnosus Lcr35 augmented the number of stools and reduced the number of hard stools. Again, although the results were statistically significant, the overall effects were clinically modest. All of the conclusions are based on single studies, some of which had a very small number of participants and methodological limitations; thus, the conclusions should be interpreted with great caution. Repeat studies with the probiotic strains that have been proven effective are needed. A paucity of data did not allow us to con-
include whether any particular probiotic is more effective than another.

**Previous reports**

Previously, one systematic review[18], co-authored by one of the authors of the current review, aimed at determining the effect of probiotics on constipation was performed. This systematic review, published in 2005 (search date: January 2004), identified two RCTs with a total of 140 adult participants. It was concluded that the administration of two probiotic strains (E. coli Nissle 1917, L. casei Shirotai) significantly improved stool frequency and consistency, with no difference in the degree of bloating or flatulence; no adverse effects were reported. Our updated results include results from more RCTs, thus, more precisely define the effects of using probiotics for the treatment of constipation.

Evidence from non-RCTs suggests that at least some probiotics may be effective. For example, in children with constipation defined according to the Rome III criteria, the administration of Bifidobacteria (B. bifidum, B. infantis, and B. longum) and Lactobacilli (L. casei, L. plantarum, and L. rhamnosus) to 20 children aged 4-16 years resulted in an increased frequency of bowel movements, a decreased number of faecal incontinence episodes, and reduced abdominal pain, although there was no change in stool consistency[19]. In adults, preliminary data from a non-RCT revealed that the administration of L. rhamnosus and Propionibacterium freudenreichii resulted in a small, but significant, increase in defecation frequency[20]. However, this result was only true if the probiotics were administered together and not if only a single strain was given.

**Mechanism of action**

Mechanisms by which probiotics might work in the treatment of constipation have been briefly discussed in the Introduction section. Clearly, they are not well understood. Perhaps the best mechanism documented is the mechanism by which B. animalis DN-173010 exerts its effects. In healthy subjects, several RCTs have evaluated the effect of B. animalis DN-173010 on colonic transit times. One double-blind RCT conducted in 72 healthy adults (aged 21-42 years) used radio-opaque pellets to measure colonic transit times. This study revealed a statistically significant reduction in the total colonic transit time of 21% (men: P < 0.03, women: P < 0.05) and a reduction in the sigmoid transit time of 39% (P = 0.02), particularly in women, with probiotic treatment. However, the beneficial effect was limited to the subjects who received living B. animalis DN-173010 and was not observed in those who received heat-treated B. animalis DN-173010[21]. Another double-blind RCT performed in 36 healthy women (aged 18-45 years) revealed significantly shorter total colonic and sigmoid colonic transit times (P < 0.05) following ingestion of 375 g/d of a fermented milk containing yoghurt cultures plus B. animalis DN-173010 for 10 d, compared with the transit times observed with ingestion of the control probiotic-free product[22]. Two further non-blind RCTs were carried out in healthy elderly subjects who were divided into groups according to their different baseline colonic transit times. Both studies demonstrated a reduction in transit times in all of the groups compared with baseline with consumption of fermented milk containing B. animalis DN-173010[23,24]. Further studies are needed to confirm these findings.

**Strengths and limitations**

The advantage of any systematic review is the low risk of subjective data selection. Study searches, assessment, and data synthesis were all based on predefined criteria and were performed with the use of well-established repetitive tools by two reviewers independently. Nevertheless, our analysis has some limitations. First, we cannot fully exclude publication bias, i.e. publication or non-publication of data depending on the results, with negative findings being less likely to be published irrespective of the methodological quality. As studies involving the administration of probiotics are often supported by the manufacturers, the possibility remains that negative results remain unpublished. No sufficiently effective strategy of identifying such studies has been developed. Second, even though no language limitation was imposed, in practice it was not feasible to assess data from reports written in Japanese. Third, any systematic review is only as good as the constituent studies. Only some of the trials included in our analysis seemed methodologically sound. Potential limitations included unclear or inadequate allocation concealment, no intention-to-treat analysis, and no blinding. Fourth, some trials included a small sample size. Finally, the effects of probiotics are strain specific as well as population specific. While a systematic review or a meta-analysis on probiotics does provide valid information, caution should be exercised in not over interpreting the results of a meta-analysis, particularly when all probiotics have been evaluated together.

**Safety issues**

In general, the safety profile of probiotics seems to be good. In the included trials, no adverse effects were noted. The safety issue is important, as based on the available literature there is concern that the use of probiotics in at-risk populations may result in harmful events. Most complications have occurred in immunocompromised subjects or in patients with other life-threatening illnesses, who were managed in intensive care units and treated with probiotics.

In summary, this systematic review demonstrates that the data published to date do not yet provide sufficient scientific evidence to support a general recommendation about the use of probiotics in the treatment of functional constipation. Until such data are available, we believe that the use of probiotics for this condition should be considered investigational. Also, we believe that our demonstration of clinical uncertainty about this issue is
an important finding. As pointed out by Alderson and Roberts[25], clinical uncertainty is a prerequisite for the large-scale RCTs needed to evaluate the influence of such interventions; it also helps to clarify available treatment options and stimulate new and better research.

COMMENTS

Background
Probiotics are increasingly being used in pediatric population. However, there is still uncertainty regarding the use of probiotics for the treatment of constipation.

Research frontiers
Until more data are available, the use of probiotics for the treatment of constipation condition should be considered investigational. The large-scale RCTs are needed to evaluate the effect of specific probiotic strain(s) for the treatment of constipation.

Innovations and breakthroughs
The updated results include results from more RCTs; thus, more precisely define the effects of using probiotics for the treatment of constipation.

Applications
Until such data are available, the use of probiotics for this condition should be considered investigational. The large-scale RCTs are still uncertainty regarding the use of probiotics for the treatment of constipation.

Peer review
This manuscript describes a systematic review of randomised controlled trials that evaluated the efficiency of probiotics in the treatment of functional constipation.

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