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McFarland LV, Karakan T, Karatas A. Strain-specific and outcomespecific efficacy of probiotics for the treatment of irritable bowel syndrome: A systematic review and meta-analysis. EClinicalMedicine. 2021 Oct 18;41:101154.

What We Know, Think We Know, or Are Starting to Know

The market for probiotics continues to be one of the most lucrative in the health and dietary supplements category, valued at \$61-billion U.S. dollars in 2021 and projected to grow by 7% over the remainder of the decade. Of course, commercial viability and evidence of efficacy are mutually exclusive concepts in the business of health and wellness.

The International Scientific Association for Probiotics and Prebiotics [ISAPP] defines probiotics as: *"live microorganisms that, which administered in adequate amounts, confer a health benefit on the host"* ⁽¹⁾. There is a key aspect to these criteria; the definition is strain-specific, and only applies to specific strains that have evidence from randomised controlled trials [RCTs] demonstrating a positive effect ⁽¹⁾.

Of bacterial species with some evidence from RCTs supporting a benefit, the *Bifidobacterium* and *Lactobacillus* families are broadly the most popular used as probiotics, as they confer core benefits to host health that are attributable to the species, e.g., selective fermentation of dietary fibres ^(1,2). Most of the evidence for probiotic strains is in relation to gastrointestinal [GI] infections, particularly GI infections characterised by diarrhoea ^(3–5).

What about Irritable Bowel Syndrome [IBS]? Individuals with IBS display altered bacterial composition in the gut compared to healthy controls, and lower levels of bacterial species that specialise in the breakdown of 'prebiotic' fibres, including *Bifidobacteria* ⁽⁶⁾. However, undertaking a low FODMAP diet for IBS, since FODMAPS are also prebiotic fibres, has the effect of lowering levels of *Bifidobacteria* in the gut ⁽⁷⁾.

Given this altered microbial landscape associated with IBS, could probiotic supplementation be helpful for this condition? The present study is the most recent meta-analysis on this question.

The Study

The investigators conducted a systematic review and meta-analysis of probiotic studies in IBS, using the following criteria:

- **Population**: Adults or paediatric patients with a diagnosis of IBS.
- **Design**: RCTs with a minimum of 2 trials on the same probiotic strain.
- **Intervention**: Either single-strain or multi-strain probiotics using ISAPP definition of 'probiotic'.
- **Control**: Either standard care/treatment controls or a placebo control group.
- **Duration**: Not specified.

• **Outcomes**: The main outcomes were changes in the global IBS-Symptom Severity Score [IBS-SSS]; changes in abdominal pain scores; frequency of abdominal pain relief; change in bloating scores.

The analysis included several subgroup considerations, including subtype of IBS [IBSconstipation dominant (IBS-C), IBS-diarrhoea dominant [IBS-D], or mixed constipation/ diarrhoea [IBS-M], the dose of probiotic, and adult or paediatric participants.

The outcomes were presented as standardised mean difference [SMD; i.e., effect sizes] and 95% confidence intervals [95% CI].

Results: 42 RCTs were included in the systematic review, of which 40 RCTs were suitable for inclusion in the meta-analyses. Two studies on the same probiotic strain [*E. coli* Nissle 1917] were excluded from the meta-analysis because they used different outcome measures. 86% of participants in the included studies were adults, and women comprised 66% of included participants.

Change in Global IBS-SSS Scores: There were six different probiotic types which had been used in ≥ 2 studies per probiotic type. The overall pooled effect of probiotic supplementation on IBS-SSS scores was an SMD of -2.39 [95% CI, -1.46 to -3.32], indicating a very large effect size for reducing global IBS symptom scores.

Of the included specific probiotic types, *Bifido. infantis* 35624 and a 7-strain commercial probiotic called "DuoLac®" showed the largest effect sizes, however, the effect size for *B.Infantis* was driven entirely by a single study. The strain *Bac. coagulans* MTCC5260 and a 4-strain probiotic also showed significant reductions in IBS-SSS scores with large effect sizes.

Change in Abdominal Pain Scores: For this outcome, there were 12 different probiotic types which had been used in ≥ 2 studies per probiotic type. The overall pooled effect of probiotic supplementation was an SMD of -1.47 [95% CI, -0.99 to -1.95], indicating a very large effect size for abdominal pain scores.

Of the 12 different probiotics, significant reductions in abdominal pain scores were shown, in order of effect size, for the 7-strain "DuoLac®" formula, the single-strain *L. rhamnoses GG*, the single strain *Bac. coagulans* MTCC5260, and the 8-strain "VSL#3®".

Change in Bloating Severity Scores: For this outcome, only four probiotics had been used in ≥2 studies, and there was no significant overall effect size for probiotic supplementation on bloating severity scores. There was also no significant effect size for either the two single-strain probiotics or two multi-strain probiotics used in the included primary studies.

Subgroup Analysis – IBS Subtypes: Of the included studies, only eight RCTs were suitable for this subgroup analysis. In this analysis, the 7-strain "DuoLac®" formula significantly reduced abdominal pain in individuals with IBS-D, with a very large effect size. However, no probiotic strain was shown to reduce abdominal pain scores in participants with IBS-C.

The Critical Breakdown

Pros: The study protocol was preregistered with PROSPERO, the preregistration database for systematic reviews. Relevant databases were searched, and the publication date for included studies extended up to June 2021. Primary studies were only included if the probiotic used in that study met ISAPP definition for a probiotic. Each probiotic included was also required to have minimum of 2 RCTs using the same probiotic and with at least one similar outcome measure. This made the best of an incoherent area of evidence, attempting to bring some degree of uniformity to the exposure-outcome relationships being analysed. The main strength of this meta-analysis is its specific consideration of strain-specific effects of probiotics [more under *Key Characteristic*, below].

Cons: The sample sizes and duration of included trials were not clearly stated. The inconsistency in the outcome measures of the primary included studies limits the strength of the meta-analysis by confining the analysis of specific strains on specific outcomes to a limited number of studies. The lack of a defined common outcome is a limitation of this research area. There was insufficient consideration of the IBS subtypes in the included studies. There was also very high heterogeneity between the included studies, indicating substantial variability in the included data. This may reflect the diverse array of included probiotics, which may limit wider generalisability beyond specific outcomes.

Key Characteristic

The overall theory within the probiotic literature has been that the potential benefits of probiotic supplementation may be both strain and condition specific, but particularly strain-specific ⁽⁸⁾. The key characteristic of the present meta-analysis was therefore the consideration of strain-specific effects of the probiotics, for which a minimum of ≥ 2 RCTs were required on a specific probiotic strain type [including multi-strain formulations].

A limitation of previous meta-analyses in this area has been that pooling data in a metaanalysis may yield misleading results if the included studies investigated different strains in different gastrointestinal conditions, and then sweeping conclusions of "probiotics are beneficial for IBS" are drawn ^(3,8).

One previous 2016 meta-analysis did attempt to distinguish by probiotic strains, but only distinguished between single-strain or multi-strain probiotic formulas ⁽⁹⁾. The present meta-analysis extends this evidential picture by providing evidence that both specific single-strain probiotics, such as *Bac. coagulans* MTCC5260, and specific multi-strain formulas such as "DuoLac®", may have some efficacy in reducing global IBS symptoms and abdominal pain.

Interesting Finding

One of the challenging aspects of the literature on probiotics and GI conditions is trying to tease out a consistent signal from the noise of the data. In this regard, it was interesting to see consistency in effects of specific probiotics across a couple of main outcomes in the present study.

Of particular interest was the effects of the single-strain probiotic *Bac. coagulans* MTCC5260, which showed a very large effect size in reducing global IBS symptoms and

abdominal pain. A 2018 pilot trial using *Bac. coagulans* MTCC5260 showed improvements in IBS quality of life ratings, however this trial was conducted in individuals with diagnosed major depressive disorder, which may itself relate to GI symptoms ⁽¹⁰⁾.

The two studies included in the present meta-analysis on *Bac. coagulans* MTCC5260 were conducted each in adults and in children aged 4 to 12yrs, indicating that this single-strain probiotic may benefit IBS in adult and paediatric populations. In the analysis on bloating severity, the overall effect size for *Bac. coagulans* MTCC5260 indicated a benefit, albeit the finding was not statistically significant.

However, a recently published intervention trial in adults with gastrointestinal bloating and gas, but without a diagnosis of IBS, also showed significant effects of this probiotic strain on gastrointestinal symptoms ⁽¹¹⁾. Overall, the evidence appears to lean toward strain-specific efficacy for *Bac. coagulans* MTCC5260 as a single-strain probiotic for IBS and GI distress, albeit the evidence remains limited.

Relevance

The evidence and recommendations for probiotics in the management of IBS has been based on broad generalisations. For example, the 2016 British Dietetic Association review and practice guidelines for the use of "probiotics" in IBS made no specific recommendations based of variability between probiotic strains and outcomes ⁽¹²⁾.

A more recent 2021 update from the British Society of Gastroenterology recommended that probiotics as an overall class of supplement may be recommended to patients with IBS, but that the evidence did not support strain-specific recommendations ⁽¹³⁾.

Does the present meta-analysis take the evidence that extra step forward toward strain-specific recommendations? Not quite. Although the approach to the analysis is commendable, the investigators were limited by the heterogeneity of the evidence, and no strain-specific analysis had more than four RCTs included.

In fact, most of the large effect sizes shown were from strain-specific meta-analyses with two to three RCTs. This isn't a particularly persuasive body of evidence, although it certainly does tip the balance of the evidence toward a beneficial effect of probiotics in the management of IBS. Of particular note is that, consistent with a previous meta-analyses ^(3,9), it does appear that both single-strain and multi-strain probiotics may exert benefits.

Application to Practice

Ultimately, the evidence for strain-specific efficacy, whether a single-strain or multistrain formula, from the present study is confined to a small number of studies. However, the relevant question for practitioners is whether probiotics may be recommended for IBS management, and the current evidence, including the recent British Society of Gastroenterology IBS guidelines, does support the recommendation of probiotics for IBS.

What is less clear is whether a strain-specific recommendation can be made, and the overall quality of evidence is weak. A prudent approach would be to opt for a commercially available probiotic with evidence of efficacy. For example, *L. rhamnoses*

GG, DuoLac®, and *Bac. coagulans* MTCC5260 [commercially sold as Unique IS2TM], are all commercially available.

A trial of 8 to 12-weeks supplementation with one probiotic could be attempted, with supplementation discontinuing if no symptom improvements were noted in that timeframe. It would of course be possible to attempt another probiotic strain, but be mindful for your patients/clients that these are not cheap supplements.

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