OPTIMIZING WITH PROBIOTICS
DIGESTIVE HEALTH

By Lori Lathrop Stern, PhD, RD, Science Liaison, IFF

The commensal organisms within the gastrointestinal tract collectively represent one of the most important determinants of digestive health and overall wellbeing. A better understanding of the dynamic relationships between the microbiota, the gut mucosa, and the gastrointestinal immune system, opens new approaches for addressing common digestive health concerns and functional bowel disorders.

Over the past 30 years, microbiome researchers have generated a base of evidence showing that supplementation with certain probiotics can affect colonic transit time (Waller PA, et al. *Scand J Gastroenterol*. 2011), influence the GI immune system (Cheng J, et al. *Front Nutr.* 2021) and affect bowel movement frequency (Ibarra A, et al. *Gut Microbes*. 2018). In some cases, particular probiotics may counter the negative GI effects of antibiotics (Ouwehand AC, et al. *Vaccine*. 2014).

There's also evidence that specific probiotics and their metabolites can influence expression of mu opioid receptors in the gut mucosa (Ringel-Kulka T, et al. *Aliment Pharmacol Ther*. 2014), an aspect of the Gut-Brain axis with significant clinical implications.

The Gut-Brain axis has grabbed media headlines recently, but there are also lesser-known axes between the gut and the skin, the lungs, the liver, the joints, and the muscles, explains Arthur Ouwehand, PhD, adjunct professor of microbiology at the University of Turku, and one of the world's experts on probiotics and their impact on human health.

All of these axes can be affected—positively or negatively—by the gut microbiota. This means that balancing the gut microenvironment and optimizing digestive health will have ripple effects through multiple organ systems.

"With digestive health people are usually thinking about things like bowel function and diarrhea. However, the intestine is connected to many other organ systems through hormonal, neurological, and immunological pathways. Digestive health is therefore key to general health," says Dr. Ouwehand, who is also a Technical Fellow at Global Health & Nutrition Sciences, International Flavors and Fragrances (IFF), Kantvik, Finland. IFF's HOWARU® line of proprietary probiotics includes some of the most well-researched probiotic strains in the world.

"All the other organ systems are related to the gut. They influence the gut and the gut influences them. Those relationships may be direct or indirect."

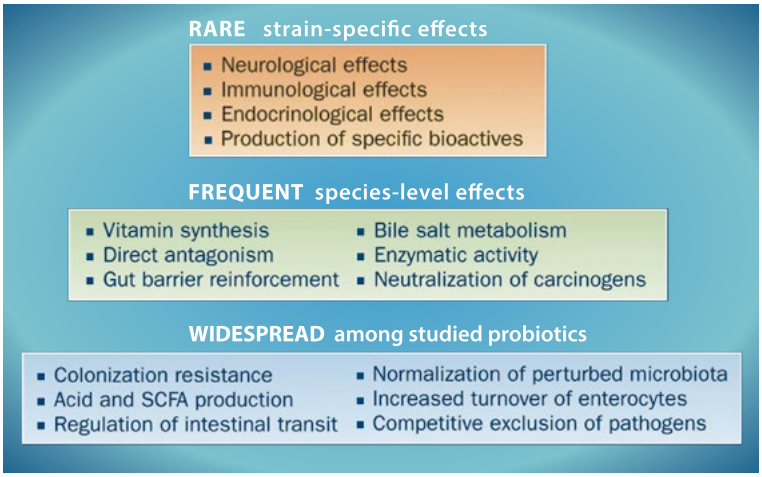


Fig. 1: Probiotics benefit humans in diverse ways. Some of their effects are common to a wide range of organisms, while others are species- and strain-specific.

Adapted from International Scientific Association for Probiotics & Prebiotics 2014 consensus statement on the scope and appropriate use of the term probiotic.

A Completely Different Approach

When considering probiotics from a clinical perspective, it is important to recognize that they are not like drugs that target specific biochemical pathways in a binary "agonist/antagonist" manner, explained Dr. Ouwehand. Rather, they affect a wide range of cell types and physiologic pathways, producing multiple effects.

The same probiotic strain can have seemingly opposite effects. For example, in the context of antibiotic-associated diarrhea, a certain strain may be helpful in slowing gut transit time and reducing bowel movement frequency. Yet in the context of constipation, the same strain may speed transit time and increase frequency, says Dr. Ouwehand.

That may seem paradoxical if one is thinking from the perspective of "discrete mechanisms of action" as applied to pharmaceuticals. But it makes sense if one keeps in mind that probiotics facilitate changes in the microbial ecosystem.

"Probiotics tend to normalize things," Dr. Ouwehand says. "It's about balancing back to a normal state. Probiotics are not like drugs that push only in one direction. A laxative is always a laxative. It always pushes in the same direction whether necessary or not. But probiotics push toward the middle, toward balance."

Johanna Maukonen, Dsc (Tech), IFF's Director of Global Clinical Innovation & Translation, emphasizes that probiotics are for enhancing health, not curing diseases. "This is a completely different approach. Probiotics do not provide immediate symptom relief. They're not like ibuprofen or aspirin, where you take them to treat a particular symptom. They are for facilitating digestive health."

That said, a meta-analysis of 84 clinical trials involving well over 10,000 patients showed that probiotics, "are generally beneficial in treatment and prevention of gastrointestinal diseases" (Ritchie ML, Romanuk TN, *PLoS ONE*. 2012).

The disorders covered by this metanalysis were: Pouchitis, Infectious diarrhea, Irritable Bowel Syndrome, *Helicobacter pylori*, *Clostridioides difficile* Disease, Antibiotic Associated Diarrhea, Traveler's Diarrhea, or Necrotizing Enterocolitis. In aggregate, the 84 trials looked at 11 different organisms alone or in various combinations. The authors, based at Dalhousie University, Halifax, note that there was a 42% risk reduction across all eight diseases studied.

What is a "Healthy" Gut?

In their excellent review of the science on *Bifidobacterium animalis* subsp. *lactis HN019* (*B. lactis HN019*™)—one of HOWARU®'s leading strains—Jing Cheng, PhD, and colleagues define gut health in terms of intact epithelial barrier function, homeostatic intestinal microbiota, optimal functioning of the stomach, liver, gallbladder, pancreas and intestines, and optimal gut motility.

"The interactions of those systems are in homeostasis in healthy subjects with normal bowel function and balanced immune function. However, this can be perturbed by antibiotic usage, unbalanced diet, and other life-style factors, infections, and other disease conditions. This may lead to changes in bowel habits and stool consistency, diarrhea, constipation, or a spectrum of both of them, such as manifested in different subtypes of irritable bowel syndrome" (Cheng J, et al. *Front Nutr*. 2021).

Intestinal barrier integrity, "is a prerequisite for homeostasis of mucosal function," write Cheng and colleagues.

Increased intestinal permeability is associated with mucosal inflammation, which is a factor in many disorders including inflammatory bowel disease (IBD), celiac, irritable bowel syndrome (IBS), and obesity (Bischoff SC, et al. *BMC Gastroenterol*. 2014). Maintaining or restoring mucosal integrity is, therefore, an important clinical objective.

Equally important is optimizing motility. As Dr. Cheng points out, "the link between the gut dysmotility related disorders and dysfunctional-intestinal barriers has led to a hypothesis that certain probiotics could help in normalizing gut motility and maintaining gut health."

"If you've been constipated, and you're having some improvements in transit time, you are aware that 3 or 4 defecations per week is better than 1 or 2. That's enhancing health, and it is directly relevant in your life," says Dr. Maukonen.

Core Benefits of Probiotics

In 2001, an expert panel convened by the World Health Organization's Food and Agriculture Organization (FAO) published a formal definition of probiotics as: "live microorganisms which, when administered in adequate amounts, confer a health benefit on the host."

Twelve years later, the International Scientific Association for Probiotics and Prebiotics (ISAPP) held a consortium that included gastroenterologists, pediatricians, primary care doctors, and immunologists, as well as microbiologists, geneticists, and food scientists to review more than 8,000 studies and metanalyses. The consortium reaffirmed the WHO/FAO definition (with minor grammatical changes), and *categorized the clinical benefits of probiotics* according to the degree to which they are common to many organisms or unique to particular species and strains (Fig. 1).

- **"Widespread" effects** common to many organisms include: Colonization resistance; Production of short chain fatty acids; Regulation of intestinal transit; Normalization of perturbed microbiota; Increased turnover of enterocytes; Competitive exclusion of pathogens.
- **"Frequent" effects** that tend to be species-specific include: Vitamin synthesis; Direct antagonism; Reinforcement of gut barrier function; Bile salt metabolism; Enzymatic activity; Neutralization of carcinogens.
- **"Rare" effects** that are highly strain-specific include: Neurologic, immunologic, and endocrine effects, as well as production of specific bioactive compounds (Hill C, et al. *Nature Rev Gastroenterol*. 2014).

Microbiota Across the Lifespan

The gut microbiota tends to change as people age, and usually for the worse, according to Drs. Timothy "Ted" Dinan and John F. Cryan of the APC Microbiome Institute, University College Cork, Ireland. The APC Microbiome Institute is one of the world's leading research centers, and Drs. Dinan and Cryan have been at the forefront of the field for decades.

They note that aging is associated with "a narrowing in microbial diversity," and especially a decline in friendly bifidobacteria (Dinan TG, Cryan JF. *J Physiol*. 2016). High microbial diversity in the gut is considered a hallmark of overall health in adults, while diminished diversity correlates with declining health status.

In a study of fecal samples from 178 elders, Claesson and colleagues found a relationship between microbiome changes, markers of inflammation, and frailty. Loss of diversity was especially pronounced among frail residents of long-term care facilities (Claesson MJ, et al. *Nature*. 2012).

In their 2015 review, Drs. Paul O'Toole and Ian Jeffery assessed a wide range of studies showing that the gut microbiota of older people differs from that in young adults. But they stress that the microbial changes are gradual; there is no sudden shift occurring at a particular age threshold (O'Toole PW, Jeffery IB. *Science*. 2015).

Though incremental, age-associated microbial changes have far-reaching impact. "The microbiota may modulate aging-related changes in innate immunity, sarcopenia, and cognitive function, all of which are elements of frailty" (O'Toole PW, Jeffery IB. *Science*. 2015).

University of Helsinki researchers analyzed the microbiota of 72 elders with Parkinson's disease (PD), compared with 72 matched controls. They found marked reductions in levels of *Prevotellaceae* in the PD patients. There was also a correlation between elevated levels of *Enterobacteriaceae* and severity of postural instability and impaired gait (Scheperjans F, et al. *Movement Disord*. 2014).

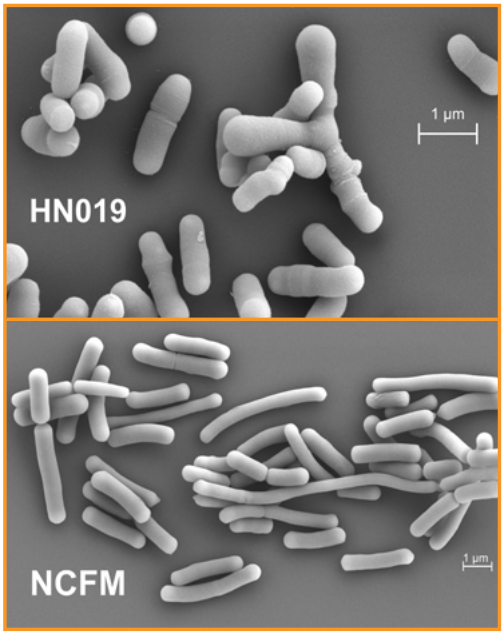
Researchers at Rush University, Chicago, looked at sigmoid biopsies and fecal samples from 38 PD patients, and 34 healthy controls. They saw consistently lower levels of butyrate-producing organisms, specifically *Blautia*, *Coprococcus* and *Roseburia*, in the PD group, along with an increase of pro-inflammatory *Ralstonia* species. The authors concluded that there is a "proinflammatory dysbiosis" that might play a role in the etiology of PD (Keshavarzian A, et al. *Movement Disord*. 2015).

Drs. Dinan and Cryan point out that there is still considerable debate about whether or not changes in the gut microbiota play a causal role in diseases of aging. The available data suggest that neuropsychiatric disorders of aging "might be treated in the future by targeting the microbiota either by microbiota transplantation, antibiotics or psychobiotics" (Dinan TG, Cryan JF. *J Physiol*. 2016).

One of the most consistent age-associated microbiota changes is a decline in intestinal bifidobacterial species. Researchers at Massey University, Palmerston North, NZ, suggest that it is possible to rectify this via supplementation with *B. lactis* HN019™. They randomized 80 healthy volunteers over age 60 years, to either placebo or three different doses of the probiotic: 5×10^9 CFU/day (high dose); 1×10^9 CFU/day (medium dose), or 6.5×10^7 CFU/day (low dose) in a carrier of 250 mL reconstituted skim milk.

Compared with the placebo, all three dose levels raised bifidobacteria in fecal samples, while simultaneously reducing enterobacteria. The investigators also saw increases in beneficial lactobacilli and enterococci with all three dose levels. "*B. lactis* HN019 is a suitable probiotic for elderly human subjects and even the lowest dose tested (6.5×10^7 CFU/day) is able to confer desired changes in the intestinal microflora," the authors conclude (Ahmed M, et al. *J Nutr Health Aging*. 2007).

According to Dr. Cheng and colleagues, *B. lactis* HN019™ supports normal physiological function in immunosenescent elderly and excludes potential pathogens. Since bifidobacteria in general are able to digest oligosaccharides and other types of fiber without producing a lot of gas, "the use of *B. lactis* HN019, could divert the fermentation in the colon toward non-gaseous end-products" (Cheng J, et al. *Front Nutr*. 2021). This would be an obvious benefit for elders with excessive flatulence.



Figs 2A & 2B: Above: *Bifidobacterium animalis* subsp. lactis HN019 (*B. lactis* HN019™). Below: *Lactobacillus acidophilus* NCFM®. *©IFF, Finland, 2021 (FESEM imaging VTT)*

Probiotics and Antibiotics

When used judiciously, antibiotics reduce the morbidity and mortality of a wide range of bacterial infections. But gastrointestinal disturbances, especially antibiotic-associated diarrhea (AAD), are a common consequence.

The incidence of AAD ranges between 5–35% of all patients taking antibiotics, according to a 2008 review by Veterans Affairs researcher, Lynn McFarland, PhD (McFarland LV. *Future Microbiol*. 2008). A more recent observational study of over 2,500 inpatients at four Belgian hospitals showed an AAD rate of 9.6% (Elseviers MM, et al. *BMC Infect Dis*. 2015). Incidence varies by antibiotic type, duration of treatment, pathogen being treated, and overall patient health status.

Given that global antibiotic use rose by 65% from 2000 to 2015 (Klein EY, et al. *PNAS*. 2018), and has shown no sign of slowing since then, AAD will remain a common problem worldwide—one that can add significantly to medical costs.

In their hospital-based study, Prof. Monique Elseviers and colleagues noted that each case of AAD required roughly one hour of additional nursing care per patient per day. "Preventive actions are highly recommended to reduce the prevalence of AAD and associated healthcare costs," they wrote (Elseviers MM, et al. *BMC Infect Dis*. 2015).

Antibiotic-related microbial disruptions can be slow to resolve on their own. Researchers at the Massachusetts Institute of Technology analyzed stool samples from 39 children, and found it took roughly one month for the natural restoration of pre-drug microbial diversity in the wake of antibiotic treatment (Yassour M, et al. *Sci Transl Med*. 2016).

Probiotics can help, according to IFF's Dr. Ouwehand, who notes that AAD is one of the best-documented clinical applications for probiotic interventions.

There are several large meta-analyses on this subject, showing that probiotics could reduce the overall risk of AAD by 44–57%, and the risk of *C. difficile*-associated diarrhea by 41–71% (McFarland LV, et al. *Am J Gastroenterol*. 2006; Hempel S. et al. *JAMA*. 2012; Sazawal S, et al. *Lancet Infect Dis*. 2006).

In 2007, Dr. Anna Engelbrektson led a multicenter study looking at cell culture and microbial DNA in fecal samples from 40 adults treated with a 7-day oral course of Augmentin (amoxicillin and clavulanic acid) at 875 mg twice daily. The subjects were randomized to concurrent treatment with a maltodextrin

placebo or a five-strain probiotic combination of: *B. lactis* BI-04 (5×10^9 CFU), *B. lactis* Bi-07 (5×10^9 CFU); *Lactobacillus acidophilus* NCFM (5×10^9 CFU), *Lacticaseibacillus. paracasei* Lpc-37 (5×10^9 CFU), and *Bifidobacterium bifidum* Bb-02 (5×10^8 CFU). They took the probiotics in capsule form twice daily.

Augmentin caused significant gut microbial disturbances in both groups, indicated by relative increases in clostridium, eubacterium, bacteroides and enterobacteriaceae. But these disturbances were less pronounced in the probiotic group. Post-antibiotic fecal cultures from the probiotic patients more closely resembled baseline patterns than did those from the placebo group. The probiotic mixture prompted a more rapid return to pre-drug patterns (Engelbrektson A, et al. *J Med Microbiol*. 2009).

"This study does identify a benefit of probiotics, in part through increasing *Bifidobacterium* that may limit the disruption of gut microbiota by antibiotics," the authors write. "While this does not represent a clinical end point in itself, this study provides important insight into the nature of the disruption of gut microbiota by antibiotics and a possible mechanism whereby probiotics limit gastrointestinal adverse events."

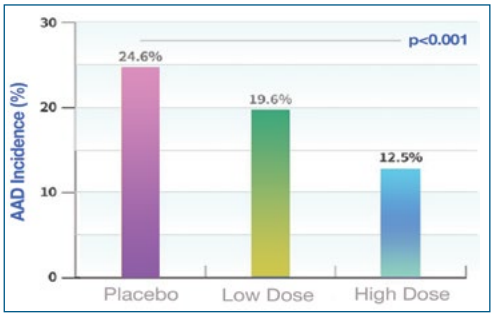


Fig. 3: Incidence of antibiotic-associated diarrhea (AAD) in subjects taking a placebo, versus low- or high-dose HOWARU® Restore probiotic. *Ouwehand AC, et al. 2014*

The Challenge of *C. difficile*

Between 10 and 25% of all AAD episodes are caused by *C. difficile*. This problematic organism has rapidly developed resistance to many common antibiotics (Spigaglia P, et al. *Adv Exp Med Biol.* 2018).

Several years after the Engelbrektson study, Dr. Ouwehand worked with researchers at Changhai Hospital in China, to study the impact of a four-strain probiotic versus placebo on the incidence of AAD, and *C. difficile*-associated diarrhea, in a cohort of more than 500 antibiotic-treated inpatients. This is the one of the largest studies ever undertaken to assess the effects of probiotics on AAD.

The antibiotics included broad spectrum penicillin, cephalosporin, and clindamycin, used to treat respiratory or urinary tract infections, or as surgical prophylaxis.

HOWARU® Restore, the probiotic tested, is a fixed combination consisting of equal amounts of: *L. acidophilus* NCFM, *L. paracasei* Lpc-37, *B. lactis* Bi-07, and *B. lactis* BI-04. Patients were randomized to placebo or to low-dose (4.17×10^9 CFU) or high-dose (1.7×10^{10} CFU) probiotics. They took their assigned treatment daily, in capsule form, roughly two hours after the morning antibiotic dose, for 10 to 21 days (depending on patient's specific condition), and continued for 7 days after the last antibiotic dose.

The impact on AAD was clear: in the placebo group 24.6% of patients developed AAD (Fig. 3), while in the high-dose probiotic group, that was nearly halved to 12.5%. In the low-dose group, 19.6% developed AAD. This indicates a dose-response effect, wrote Dr. Ouwehand (Ouwehand AC, et al. *Vaccine*. 2014).

For diarrhea caused specifically by *C. difficile*, there was a similar reduction—from 4.8% in the placebo group, to 1.8% in both probiotic groups. There did not appear to be a dose-response pattern.

"After adjustment for covariates (gender, age, and days of antibiotic use), high-dose probiotic decreased the odds of AAD incidence to 0.39 of the placebo (95% CI: 0.21–0.72; p = 0.003); while the low-dose decreased to 0.72," the authors note. They estimated that the number needed to treat to obtain a reduction in AAD was 8.4.

HOWARU® Restore also appeared to minimize the severity of AAD. The number of daily liquid stools and average duration of diarrhea were significantly lower with both the low- and high-dose probiotics versus the placebo. Incidence of fever, abdominal pain, and bloating were also lower in the HOWARU® Restore groups.

Adverse events were rare, occurring in 7.2% of the placebo patients versus 4.2% in the two probiotic groups.

The Probiotics for *C. difficile* infection in adults (PICO) study assessed the impact of HOWARU® Restore in conjunction with vancomycin or metronidazole in 33 patients with mild to moderate first-episode *C. difficile*-associated diarrhea. The patients were randomized to placebo or the probiotic, which gave a cumulative dose of 1.7×10^{10} CFU per capsule, taken daily for four weeks. They were assessed at baseline, and again at weeks four and eight.

The mean number of days with diarrhea was far lower in the HOWARU® Restore group versus the placebo (3.5 days versus 12). Median duration of diarrhea was reduced from 1.0 day for placebo to 0 days. There were only two recurrences of CDI, one in each group, over the eight-week period (Barker AK, et al. *J Antimicrob Chemother*. 2017).

"Combination probiotic treatment was associated with significant improvement in diarrhea outcomes for participants, compared with placebo," wrote the authors, based at the University of Wisconsin, Madison. "Shortening the duration of an initial CDI could allow patients to stop antibiotic therapy sooner, having considerable downstream implications for reducing antibiotic resistance."

Together or Separate?

Use of probiotics in the context of antibiotic drug treatment raises important practical questions: If antibiotics cause GI disturbance by killing "friendly" bugs, won't they also kill off the probiotics? Can probiotics and antibiotics be taken simultaneously, or should they be taken at different times of the day?

According to Dr. Ouwehand, it is a good general rule to allow a few hours' time between antibiotic and probiotic doses. But as numerous studies have shown, they can be taken concurrently, with little risk that an antibiotic will obliterate the probiotics. That's because most antibiotics are fairly specific in the types of microbes they can kill. Even broad-spectrum drugs don't kill all microbes. If they did, AAD prevalence would be far higher than it is.

Further, antibiotics work by killing metabolically active microbes. The probiotics used in supplements are generally freeze-dried, so they are metabolically quiescent when ingested, and need time to resuscitate. And some probiotic organisms may also have natural resistance to common antibiotics, though Dr. Ouwehand explained that in the organisms studied, this is not a trait that is transferrable to other bugs.

Sofia Forssten, PhD, and colleagues studied fecal samples from 96 patients treated for various common infections with broad- or narrow-spectrum antibiotics, who also took either a placebo or the four-strain HOWARU® Restore concurrently. The patients were instructed to take the assigned treatment at least 2 hours apart from the antibiotic for the duration of drug therapy, and 7 days beyond.

At the end of the treatment period, the researchers were able to detect increases in all four HOWARU® Restore strains. "Each of the four strains could be detected in the feces of patients apparently unaffected by the simultaneous consumption of antibiotics" (Forssten SD, et al. *Biomedicines*. 2020). This indicates clearly that the probiotics were able to survive antibiotic exposure.

Transit Time & Bowel Function

GI transit time is an important indicator of gut health, and disturbances of intestinal transit are associated with many functional GI symptoms. Whole gut transit time (WGTT) influences circulation of enterohepatic bile acid and steroid hormones, as well as colonic pH, and production of short-chain fatty acids. Some researchers have proposed that prolonged WGTT may increase the risk of gallstones, and possibly bowel and breast cancer (Lewis SJ, Heaton KW. *Am J Gastroenterol* 1999).

According to a 2011 study by Philip Waller, MD, and colleagues, daily supplementation with *B. lactis* HN019™ can reduce WGTT. The investigators randomized 100 subjects (mean age: 44 years; 64% female) with a range of functional GI symptoms to a placebo or to *B. lactis* HN019™ at daily doses of either 17.2×10^{10} CFU (high dose) or 1.8×10^9 CFU (low dose) for 14 days.

Subjects ranged in age from 25–65 years and reported having stool types 2–4 on the Bristol Stool Chart, and an average of 1–3 bowel movements per week. At the outset, they ceased using laxatives, fiber, probiotics, or other products that might affect WGTT.

Both probiotic groups showed statistically significant reductions in WGTT, as measured by abdominal x-ray techniques, from a mean of 49 ± 30 hours down to 21 ± 32 hours in the high dose group, and from a mean of 60 ± 33 hours down to 41 ± 39 hours in the low-dose group. The placebo group showed no such change (43 ± 31 hours to 44 ± 33 hours). Waller and colleagues calculated that at the high-dose, *B. lactis* HN019™ reduced transit time by 33%, while the low dose reduced it by 25% (Waller PA, et al. *Scand J Gastroenterol*. 2011).

Both probiotic groups showed a combined two-fold decrease in frequency of upper and lower GI symptoms, which included constipation, diarrhea, irregular bowel movements, and flatulence. Those in the high-dose group had improvements in 8 of 9 symptoms measured, while those in the low-dose group had improvements in 7 of the 9. There were minimal symptom improvements in the placebo group.

"*B. lactis* HN019™ is potentially advantageous since this single product may be used to alleviate multiple gastrointestinal symptoms simultaneously," the authors concluded.

Alvin Ibarra, PhD, and colleagues randomized 228 adults with functional constipation according to the Rome III criteria, to treatment with a placebo or *B. lactis* HN019™ at a dose of 10^9 CFU (low) or 10^{10} CFU (high) per day, for a total of 28 days.

In contrast to the Waller data, they saw no significant differences in colonic transit time (CTT) between the placebo or the probiotic at either dose level. Likewise, there were no major differences between the groups on patient self-assessments of constipation symptoms, quality of life, or bowel function.

However, there was a significant increase in bowel movement frequency among a subset of 65 patients who had more severe baseline constipation—indicated by having fewer than 3 bowel movements per week. In this subgroup, the high dose probiotic increased the number of weekly bowel movements by approximately 2, compared to the placebo (Fig. 4). The low dose probiotic increased the number by approximately 1.7 over the placebo (Ibarra A, et al. *Gut Microbes*. 2018).

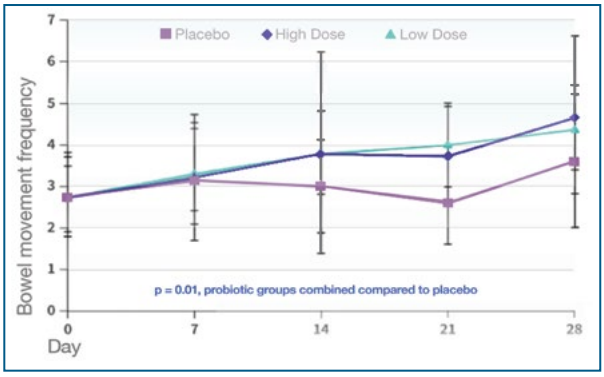


Fig. 4: Bowel movement frequency in subjects taking placebo versus low- or high-dose *B. lactis* HN019™) probiotic for 28 days. *(Ibarra A, et al. 2018)*

"HN019™ is well tolerated and improves bowel movement frequency in adults with low stool frequency," Dr. Ibarra and colleagues reported.

They acknowledge that the absence of an effect on CTT was surprising in light of the earlier Waller trial, but did not offer an explanation, other than to suggest that differences in treatment protocols (28 days in the Ibarra study versus 14 days in the Waller study), and patient populations (mostly French versus mostly African-American and Hispanic-American) might account for the differences in outcomes.

Several studies have looked at the impact of specific probiotics on functional GI symptoms in patients with IBS, and the results have been variable.

Researchers at the University of North Carolina (UNC), Chapel Hill, reported on a cohort of 60 adults who met the *Rome II criteria* for non-constipation IBS, functional diarrhea, or functional bloating. They were randomized to placebo or a two-strain probiotic containing *L. acidophilus* NCFM, and *B. lactis* Bi-07. The probiotic provided a combined total of 10^{11} CFU per pill. Patients took their assigned treatment twice daily for 8 weeks.

Overall GI symptom burdens, quality of life scores, and satisfaction with treatment improved in both groups, with no major differences between the probiotic and the placebo. However, a more detailed analysis showed that bloating was significantly reduced in the probiotic group, compared with the placebo. At 4 weeks, the mean bloating/distention scores were 4.1 (±3) for the probiotic, versus 6.17 (±3) for the placebo. That difference persisted at 8 weeks (Ringel Y, et al. *J Clin Gastroenterol*. 2011).

Anna Lyra, PhD, and colleagues studied 340 adults with IBS (constipation-predominant, diarrhea-predominant, or mixed type), who were randomized to placebo or *L. acidophilus* NCFM alone, at a dose of 10^9 or 10^{10} CFU per day, for a total of 12 weeks.

All three groups showed improvements in total IBS Symptom Severity Scores (IBS-SSS), with scores declining by a mean of 44 (±80) in the placebo group, by 50 (±82.4) in the low-dose group, by and 48.3 (±72.2) in the high dose group. Differences between the groups were not statistically significant. Likewise, there were no significant differences on self-assessed measures of defecation frequency, stool consistency, anxiety, or depression (Lyra A, et al. *World J Gastroenterol*. 2016).

However, the investigators did observe a significant decrease in abdominal pain in subjects who had moderate to severe baseline pain levels. The pain scores dropped by a mean of 20.8 points, 29.4 points, and 31.2 points in the three groups, respectively.

Probiotics & the Gut-Brain Axis

One of the most promising lines of microbiome research in recent years points to the possibility that certain probiotic strains can affect expression of endogenous opioid and cannabinoid receptors in the gut mucosa.

Prompted by positive results in animal experiments, the UNC Chapel Hill group randomized 20 women with mild to moderate recurrent abdominal pain to treatment with *L. acidophilus* NCFM alone, at a total daily dose of 2×10^{10} CFU, or a dual strain blend containing the *L. acidophilus* NCFM as well as *B. lactis* Bi-07, also at 2×10^{10} CFU per day. Patients took the assigned probiotics for 21 days. At baseline, the patients experienced pain at a level of 3–7 on a10-point Likert scale, for at least 3 out of 10 days.

The researchers took colonic mucosal biopsy samples via sigmoidoscopy before initiation and immediately after cessation of the probiotic treatment.

PCR analysis of the tissue samples showed that thewomen taking *L. acidophilus* NCFM alone had a marked 39.9-fold increase in expression of mu opioid receptors (MOR)—the primary class of receptors for endogenous opioids like beta-endorphins and enkephalins (Ringel-Kulka T, et al. *Aliment Pharmacol Ther*. 2015). MORs play an important role in regulating pain. The authors note that this is, "the first evidence for a probiotic effect on opioid-mediated pathways in humans."

The combination of *L. acidophilus* NCFM and *B. lactis* Bi-07 did not appear to increase MOR expression, a finding that may be attributable to a competitive inhibition of *L. acidophilus* NCFM by the *B. lactis* Bi-07.

L. acidophilus NCFM also produced a roughly 4-fold decrease in expression of cannabinoid 2 (CB2) expression, which was not seen with the combination probiotic. Dose may also have been a factor.

Though the study was not designed or powered for clinical conclusions, Ringel-Kulka and colleagues note that both probiotics lowered bowel symptom scores, and improved bowel function (bowel movement frequency, pain frequency), and overall wellbeing.

The finding that *L. acidophilus* NCFM can directly upregulate expression of colonic MORs may provide one mechanism to explain the significant reduction in visceral pain seen in the Lyra study of adults with IBS (Lyra A, et al. *World J Gastroenterol*. 2016).

Persistent abdominal discomfort is a common occurrence following colonoscopy, affecting up to 20% of all patients who undergo these procedures. Researchers at the Prince of Wales Private Hospital, Sydney, have shown that supplementation with the combination of *L. acidophilus* NCFM and *B. lactis* Bi-07 (1.25×10^{10} CFU each) could reduce the duration of post-procedural pain.

They randomized 320 patients undergoing colonoscopy with air insufflation to placebo or the probiotic combination, taken daily for 14 days following the procedures. Those taking the probiotic had fewer pain days—1.99 versus 2.78 days. A subgroup analysis showed that the probiotic effect was even greater among the patients who experienced abdominal pain prior to their colonoscopies. In this subset, the probiotic-treated patients had 2.16 post-procedure pain days versus 4.08 for the placebo group (D'Souza B, et al. *ANZ J Surg*. 2017).

Microbiome researchers are just beginning to shed light on the ways in which the gut microbiota interact with the human digestive, nervous, and immune systems. Already, the clinical implications are compelling.

Though there are some human benefits that are attributable to a wide range of probiotic species and strains, other benefits are quite specific to particular strains. Further research will, no doubt, shed more light on the unique benefits of various probiotic organisms, leading to promising new approaches for restoring and enhancing digestive health and overall wellbeing. ■

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Full references are available online.