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The effects of the multispecies probiotic mixture Ecologic®Barrier on migraine: results of an open-label pilot study

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RESEARCH ARTICLE

Abstract

Migraine prevalence is associated with gastrointestinal disorders. Possible underlying mechanisms could be increased gut permeability and inflammation. Probiotics may decrease intestinal permeability as well as inflammation, and therefore may reduce the frequency and/or intensity of migraine attacks. Therefore we assessed feasibility, possible clinical efficacy, and adverse reactions of probiotic treatment in migraine patients. 29 migraine patients took 2 g/d of a probiotic food supplement (Ecologic®Barrier, 2.5×10^9 cfu/g) during 12 weeks. Participants recorded frequency and intensity of migraine in a headache diary and completed the Migraine Disability Assessment Scale (MIDAS) and Henry Ford Hospital Headache Disability Inventory (HDI) at baseline and after 12 weeks of treatment. Compliance was measured every 4 weeks by counting the remaining sachets with probiotics. The study was completed by 27/29 (93%) patients who took 95% of the supplements. Obstipation was reported by 4 patients during the first 2 weeks of treatment only. The mean±standard deviation (SD) number of migraine days/month decreased significantly from 6.7±2.4 at baseline to 5.1±2.2 (P=0.008) in week 5-8 and 5.2±2.4 in week 9-12 (P=0.001). The mean±SD intensity of migraine decreased significantly from 6.3±1.5 at baseline to 5.5±1.9 after treatment (P=0.005). The MIDAS score improved from 24.8±25.5 to 16.6±13.5 (P=0.031). However, the mean HDI did not change significantly. In conclusion, probiotics may decrease migraine supporting a possible role for the intestine in migraine management. Feasibility and lack of adverse reactions justify further placebo-controlled studies.

Keywords: feasibility, gut permeability, headache, intestine, leaky gut, migraine, probiotics

1. Introduction

Migraine is a disabling disorder with a life time prevalence of 13-33% (Launer *et al.*, 1999). Several studies suggest that migraine can be considered as a complex neurogenic inflammatory disorder (Monteith and Goadsby, 2011; Waeber and Moskowitz, 2005; Wang *et al.*, 2010), but the pathophysiology is still not fully understood (Samsam *et al.*, 2010). Associations were found between migraine and gastrointestinal disorders including irritable bowel syndrome, inflammatory bowel disease and celiac disease (Van Hemert *et al.*, 2014). These associations have been found in two directions: migraine patients have more often gastrointestinal disorders compared with healthy controls and patients with gastrointestinal disorders more often suffer from migraine compared to control groups. These associations could be explained by an increased intestinal permeability, which could be a cause or consequence of these gastrointestinal disorders (Duerksen *et al.*, 2005; Kerckhoffs *et al.*, 2010; Piche *et al.*, 2009; Salim and Soderholm, 2011). Increased intestinal permeability can allow leakage of undigested food particles and bacterial components like lipopolysaccharides into the bloodstream; the leaky gut hypothesis (Parlesak *et al.*, 2000). These endotoxins can trigger a response provoking migraine (Covelli *et al.*, 2003; Mennigen and Bruewer, 2009). Consequently, diminishing gastrointestinal permeability may reduce the frequency and/or the intensity of migraine attacks.

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Probiotics are living microorganisms which, when administered in adequate amounts, confer a health benefit to the host (FAO/WHO, 2001; Hill *et al.*, 2014). Probiotics have been proven *in vitro* as well as *in vivo* to prevent damaging of the epithelial barrier (Ohland and Macnaughton, 2010). Furthermore, they are able to improve the epithelial barrier in several ways, depending on the used bacterial strain (Anderson *et al.*, 2010; Miyauchi *et al.*, 2012). They can increase the mucus production of the goblet cells, they are able to stabilise the tight junctions between the epithelial cells and they can enhance IgA production (Ohland and Macnaughton, 2010). Probiotics can also have an indirect effect on the resident microbiota. For example, some probiotic bacterial strains directly kill pathogenic bacteria by secreting antimicrobial factors (Liévin *et al.*, 2000). They can also compete with pathogens for binding sites on the epithelial cells (Neeser *et al.*, 2000), which improves the barrier function.

So far, no clinical randomised controlled trials studying the influence of probiotics on migraine have been published. An uncontrolled study with a combination of various bacterial strains (*Lactobacillus acidophilus* DDS-1, *Lactobacillus bulgaricus, Enterococcus faecium* and *Bifidobacterium bifidum*, strain numbers for the latter were not indicated in the publication) and vitamins, minerals, micronutrients, and herbs in 40 migraine patients demonstrated that 60% of the migraine patients experienced almost total relief from migraine attacks (Sensenig *et al.*, 2001). It remains unknown if this improvement was due to placebo effects, one or more bacteria, or due to the other nutrients.

To study the possible association between migraine, intestinal permeability and probiotics and to assess therapeutic consequences, large scale clinical studies with probiotics in migraine patients are needed. We started with an open-label pilot study with a multispecies probiotic product to assess feasibility, possible adverse reactions, and a first impression of clinical efficacy in migraine patients.

2. Materials and methods

Subjects

Participants were recruited via the recruitment database of Wageningen University, advertisements on the staff website of hospital 'Gelderse Valei' in Ede, and by advertisements on notice boards at Wageningen University. Subjects willing to participate were screened by means of a medical screening questionnaire. Subjects fulfilling the International Headache Classification (ICHD-II) criteria, aged ≥18 years, and who had at least 4 migraine attacks per month with a stable pattern were eligible for the study. Exclusion criteria were chronic headache, medication-dependent headache, or other types of headaches, the use of antibiotics up to two months before the start of the study and the use of probiotics, other than used during this study during or up to two weeks before the start of the treatment period. All participants gave their written informed consent. The pilot study was approved by the Medical Ethical Committee of Wageningen University (dossier 11/44) and was performed according to the principles of the Declaration of Helsinki.

Study design

Between February and June 2012 participants received 2 g of the multispecies probiotic product Ecologic®Barrier (Winclove Probiotics, Amsterdam, the Netherlands) daily for 12 weeks. The product (2.5×10^9 cfu/gram) contains the following bacterial strains: *Bifidobacterium bifidum* W23, *Bifidobacterium lactis* W52, *Lactobacillus acidophilus* W37, *Lactobacillus brevis* W63, *Lactobacillus casei* W56, *Lactobacillus salivarius* W24, *Lactococcus lactis* W19 and *Lactococcus lactis* W58. All these strains have been used before in different combinations in clinical trials showing a health benefit (Koning *et al.*, 2008; Lamprecht *et al.*, 2012; Niers *et al.*, 2009; Persborn *et al.*, 2013, Lamprecht, 2012). Compliance was measured every four weeks by counting the remaining sachets with probiotics.

Baseline number of migraine days per month were based on recall of the participants. At baseline and after 12 weeks of ingestion of the probiotics, the participants completed two headache questionnaires: The Migraine Disability Assessment Scale (MIDAS) and the Henry Ford Hospital Headache Disability Inventory (HDI,) to assess intensity of the migraine (Jacobson *et al.*, 1994; Stewart *et al.*, 1999). The MIDAS questionnaire assesses missed days of activity, but also days in which the productivity was reduced by at least half during the last three months. The HDI questionnaire focussed on the functional and emotional feelings about having headaches.

During the study period, the participants completed a headache diary daily. In this diary, frequency and intensity (10-point Likert scale) of migraine attacks, used medication and gastrointestinal complaints were recorded. The diaries were handed out, discussed and collected every 4 weeks.

Statistical analysis

We performed a sample size calculation based on previous drug trials aimed at reducing the number of days with migraine (Bensenor *et al.*, 2001; Diener *et al.*, 2004; Pfaffenrath *et al.*, 2002). From these studies we derived the standard deviation (SD) of the effect to be within 1.3 and 2.1 days. Using these estimates of the SD in the formula $n=7.9 \times (SD/D)^2$ (D = the expected change between baseline and 12 weeks), it was calculated that for an effect of 1 days (reduction in migraine days/month) between 15 and 35 of patients were needed (using a confidence level of 5% and a power of 80%).

The difference of the mean number of migraine days between the four week periods and the difference of outcomes of the questionnaires were analysed using the paired samples t-test as these data were normally distributed. To compare the data of the migraine patients with bowel complaints with those of the migraine patients without bowel complaints, an independent samples t-test was used. IBM SPSS Statistics (version 19; Armonk, NY, USA) was used to analyse data. Data are given as mean±SD and *P*-values of <0.05 were considered as significant in all analyses.

3. Results

Baseline data

In total, 37 patients (3 males, 34 females) showed interest in participation in the study, of which 29 persons met the in- and exclusion criteria. From the initial 29 participants, 1 male and 26 females (mean age: 41.8±14.7 years; range: 20-64) completed the study. The other two 2 participants (1 male, 1 female) dropped out; one for unknown reasons and one because he/she did not like the taste of the probiotics. Mean duration of migraine was 19±14.2 years (range: 1-60 years); 7 of the 27 (26%) participants experienced auras during their migraine attacks. In 14 of the 26 (54%) female participants, menstrual periods were accompanied by migraine. Regular gastrointestinal complaints, such as obstipation and diarrhoea, were reported by 19 (70%) of the participants. Of all sachets with probiotics, 95% were returned empty. Over each period of 4 weeks, 52% of the participants took all sachets, 44% of the participants missed 1-5 of the 28 sachets and 4% missed more than 5 sachets. Four participants noticed constipation in the first two weeks of taking probiotics. This diminished in the third week after starting the intake of probiotics.

Migraine days

At baseline, the mean number of migraine days was 6.7±2.4 days per month. After 4 weeks of oral intake of probiotics, this was 6.3±2.3 days per month, which further decreased to 5.1±2.2 after 8 weeks and to 5.2±2.4 migraine days per month after 12 weeks. In comparison to the baseline measurement, the number of migraine days during the second (5-8 weeks) and third (9-12 weeks) period were significant lower (*P*=0.008 and *P*=0.001, respectively). At the end of the intervention period, the mean number of migraine days per month was decreased with 1.5 days (23%) compared to baseline (Figure 1, individual scores from +3 migraine days to -5 days). Of the 27 participants, 18 participants improved their number of migraine days after three months compared with baseline, 5 participants showed no difference, whereas the number of migraine days was increased in 4 patients. In patients with gastrointestinal complaints this decrease did not differ significantly from those without gastrointestinal complaints (*P*>0.05, data not shown).

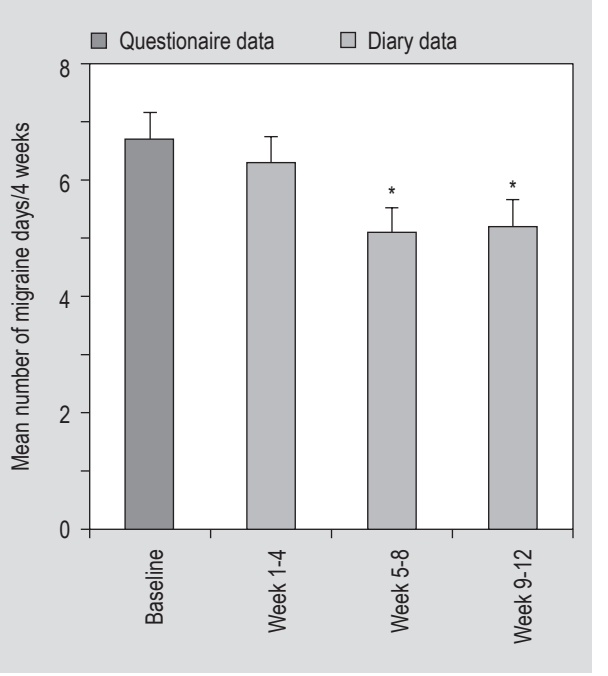

Figure 1. Mean number of migraine days per month at baseline, and after 4, 8, and 12 weeks of oral intake of probiotics in 27 migraine patients. Error bars indicate standard error of the mean. * indicates significant decrease compared with baseline (*P*<0.05).

In 18 of the 27 participants, the number of migraine days per month during the last intervention period (9-12 weeks), was lower than the baseline number of migraine days. In one participant, the migraine days increased during the intervention period. Among the remaining participants, there was no difference in the amount of migraine days per month. In four participants, the number of migraine days per month was reduced with more than 50%. Mean migraine intensity as reported in the diaries significantly decreased from 6.3±1.5 at baseline to 5.5±1.9 (*P*=0.005).

Questionnaire outcomes

At baseline, the mean HDI score was 36.3±15.4 points. After 12 weeks of oral intake of probiotics, the HDI score decreased to 33.0±6.8 points (*P*=0.252). The mean MIDAS score decreased significantly from 24.8±25.5 points to 16.6±13.5 points (*P*=0.031).

Use of medication

Except for 4 participants, every participant used migraine specific medication. During the intervention period, the use of profylaxes and triptans did not change. However, the use of over-the-counter analgesics (paracetamol, ibuprofen, aspirin) decreased from 333 dosages in weeks 1-4 to 221 in weeks 5-8 to 238 in weeks 8-12, a decrease of 29% (Table 1).

Table 1. Total number of dosages and the mean number of dosages per participant of different categories of medicines.

	0-4 weeks	4-8 weeks	8-12 weeks
Profylaxes	297.5 (mean: 11.0)	323.5 (mean: 12.0)	302 (mean: 11.2)
Triptans	98.5 (mean: 3.6)	109 (mean: 4.0)	108.5 (mean: 4.0)
Analgesics	333 (mean: 12.3)	221 (mean: 8.2)	237.5 (mean: 8.8)

4. Discussion

In this open-label pilot study, the number of migraine days and migraine associated disability decreased significantly during 12 weeks treatment with a special designed probiotic mixture. Relevant adverse reactions did not occur and compliance was high. These findings suggest that further clinical studies with probiotics in migraine patients are feasible and warranted.

During our study, we saw a slight increase in the use of migraine specific medication, however, this increase was small and unlikely to be the cause of the decrease in migraine days we observed. The use of analgesics decreased by 29%, which is in the same range as the 23% decrease in migraine days we observed.

Not all participants experienced a beneficial effect of the probiotics. In our study, 67% of the participants showed a decrease in the number of migraine days, compared to 15% who showed an increase. This is in agreement with other probiotic studies, were often responders and non-responders are found (Reid *et al.*, 2010). For instance, responder rates for irritable bowel syndrome are 18-80% (Hungin *et al.*, 2013).

The study does not prove that the probiotic itself decreases migraine because a placebo effect cannot be excluded. However, the fact that the decrease of migraine days occurred not earlier than the second treatment period (5-8 weeks) and that this decrease continued the last treatment period (9-12 weeks) suggests that the improvement is not due to placebo effects. In placebo studies, improvement during placebo usually starts soon after treatment and diminishes after some weeks of treatment (Wang *et al.*, 2012). A meta-analysis of migraine prophylaxis studies showed that the placebo-effect (percentage of patients showing a 50% improvement) was 22% while in our study this was at most 4/27=15% (Macedo *et al.*, 2008). Placebo effects are highly dependent on the expectation of the participants (Elsenbruch *et al.*, 2012), and we assume that participants expect stronger effects when they are participating in a drug trial than in a trial with a food supplement (de Groot *et al.*, 2011). The lack of difference in probiotic treatment effect between migraineurs with and without gastrointestinal complaints, found in our study, suggests that the presence of gastrointestinal complaints is not a reliable selection criterion for effective treatment with a probiotic. A better selection criterion would be the presence of increased intestinal permeability. This can be demonstrated with different tests, like the lactulose/mannitol test, or the use of radioisotope scanning tests (Scaldaferri *et al.*, 2012). Increased intestinal permeability will be a selection criteria in our further studies.

Antihypertensive and antiepileptic drugs are well known migraine prophylaxes. They decrease migraine days with 21 to 62% (Bussone *et al.*, 2005; Gales *et al.*, 2010; Holroyd *et al.*, 1991; Schellenberg *et al.*, 2008; Shuhendler *et al.*, 2009). In our study, migraine days decreased with 23%, which is within this interval. An advantage of probiotics is the lack of severe side effects. In our study the well-known and relatively mild side effects including bloating, diarrhoea, constipation and nausea (D'Souza *et al.*, 2002; Hoveyda *et al.*, 2009), disappeared within three weeks of treatment.

The strength of this pilot study is that it is the first study using probiotics in migraine patients. However, it had several limitations. Next to the lack of a placebo, we did not measure intestinal permeability at inclusion and after the intervention period. Furthermore, the type of migraine was not classified in detail and no run-in period was conducted. The number of migraine days at baseline were based on the recall of migraine attacks per month. Therefore, these indications may not be as reliable as it could be with a run-in period. However, the number of migraine days at baseline was comparable with the number of migraine days during the first four weeks of intervention which suggests that baseline data were reliable. The use of analgesics decreased during the study. However, no baseline measurement of the medication use was gathered, so these data could not be compared with the use of medication before the intervention period.

Nevertheless it can be concluded that probiotics may have a positive influence on the severity and frequency of migraine and that large scale clinical randomised placebo-controlled studies are warranted as to evaluate working mechanisms and clinical efficacy. The probiotic food supplement used in this study may decrease migraine, both in frequency and intensity. This finding supports the leaky gut hypothesis. Feasibility and lack of adverse reactions justify further placebo-controlled studies.

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Conflicts of interest

SvH is employee of Winclove b.v., producer of probiotic food supplements. The other authors report no conflicts of interests.

References

Anderson, R.C., Cookson, A.L., McNabb, W.C., Kelly, W.J. and Roy, N.C., 2010. *Lactobacillus plantarum* DSM 2648 is a potential probiotic that enhances intestinal barrier function. FEMS Microbiology Letters 309: 184-192.

Bensenor, I.M., Cook, N.R., Lee, I.M., Chown, M.J., Hennekens, C.H. and Buring, J.E., 2001. Low-dose aspirin for migraine prophylaxis in women. Cephalalgia 21: 175-183.

Bussone, G., Diener, H.C., Pfeil, J. and Schwalen, S., 2005. Topiramate 100 mg/day in migraine prevention: a pooled analysis of double-blind randomised controlled trials. International Journal of Clinical Practice 59: 961-968.

Covelli, V., Pellegrino, N.M. and Jirillo, E., 2003. A point of view: The need to identify an antigen in psyconeuroimmunological disorders. Current Pharmaceutical Design 9: 1951-1955.

D'Souza, A.L., Rajkumar, C., Cooke, J. and Bulpitt, C.J., 2002. Probiotics in prevention of antibiotic associated diarrhoea: meta-analysis. BMJ 324: 1361.

De Groot, F.M., Voogt-Bode, A., Passchier, J., Berger, M.Y., Koes, B.W. and Verhagen, A.P., 2011. Headache: the placebo effects in the control groups in randomized clinical trials; an analysis of systematic reviews. Journal of Manipulative and Physiological Therapeutics 34: 297-305.

Diener, H.C., Tfelt-Hansen, P., Dahlof, C., Lainez, M.J., Sandrini, G., Wang, S.J., Neto, W., Vijapurkar, U., Doyle, A., Jacobs, D. and Group, M.-S., 2004. Topiramate in migraine prophylaxis--results from a placebo-controlled trial with propranolol as an active control. Journal of Neurology 251: 943-950.

Duerksen, D.R., Wilhelm-Boyles, C. and Parry, D.M., 2005. Intestinal permeability in long-term follow-up of patients with celiac disease on a gluten-free diet. Digestive Diseases and Sciences 50: 785-790.

Elsenbruch, S., Schmid, J., Basler, M., Cesko, E., Schedlowski, M. and Benson, S., 2012. How positive and negative expectations shape the experience of visceral pain: an experimental pilot study in healthy women. Neurogastroenterology and Motility 24: 914-e460.

Food and Agriculture Organization of the United Nations/World Health Organization (FAO/WHO), 2001. Evaluation of health and nutritional properties of powder milk and live lactic acid bacteria. Available at: http://tinyurl.com/8bccc3r.

Gales, B.J., Bailey, E.K., Reed, A.N. and Gales, M.A., 2010. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers for the prevention of migraines. Annals of Pharmacotherapy 44: 360-366.

Hill, C., Guarner, F., Reid, G., Gibson, G.R., Merenstein, D.J., Pot, B., Morelli, L., Canani, R.B., Flint, H.J., Salminen, S., Calder, P.C. and Sanders, M.E., 2014. Expert consensus document: The International Scientific Association for Probiotics and Prebiotics consensus statement on the scope and appropriate use of the term probiotic. Nature Reviews Gastroenterology and Hepatology 11: 506-514.

Holroyd, K.A., Penzien, D.B. and Cordingley, G.E., 1991. Propranolol in the management of recurrent migraine: a meta-analytic review. Headache 31: 333-340.

Hoveyda, N., Heneghan, C., Mahtani, K., Perera, R., Roberts, N. and Glasziou, P., 2009. A systematic review and meta-analysis: probiotics in the treatment of irritable bowel syndrome. BMC Gastroenterology 9: 15.

Hungin, A.P., Mulligan, C., Pot, B., Whorwell, P., Agreus, L., Fracasso, P., Lionis, C., Mendive, J., Philippart de Foy, J.M., Rubin, G., Winchester, C. and de Wit, N., 2013. Systematic review: probiotics in the management of lower gastrointestinal symptoms in clinical practice – an evidence-based international guide. Alimentary Pharmacology and Therapeutics 38: 864-886.

Jacobson, G.P., Ramadan, N.M., Aggarwal, S.K. and Newman, C.W., 1994. The Henry Ford Hospital Headache Disability Inventory (HDI). Neurology 44: 837-842.

Kerckhoffs, A.P.M., Akkermans, L.M.A., de Smet, M.B.M., Besselink, M.G.H., Hietbrink, F., Bartelink, I.H., Busschers, W.B., Samsom, M. and Renooij, W., 2010. Intestinal permeability in irritable bowel syndrome patients: effects of NSAIDs. Digestive Diseases and Sciences 55: 716-723.

Koning, C.J., Jonkers, D.M., Stobberingh, E.E., Mulder, L., Rombouts, F.M. and Stockbrugger, R.W., 2008. The effect of a multispecies probiotic on the intestinal microbiota and bowel movements in healthy volunteers taking the antibiotic amoxycillin. American Journal of Gastroenterology 103: 178-189.

Lamprecht, M., Bogner, S., Schippinger, G., Steinbauer, K., Fankhauser, F., Hallstroem, S., Schuetz, B. and Greilberger, J.F., 2012. Probiotic supplementation affects markers of intestinal barrier, oxidation, and inflammation in trained men; a randomized, double-blinded, placebo-controlled trial. Journal of the International Society of Sports Nutrition 9: 45.

Launer, L.J., Terwindt, G.M. and Ferrari, M.D., 1999. The prevalence and characteristics of migraine in a population-based cohort: the GEM study. Neurology 53: 537-542.

Liévin, V., Peiffer, I., Hudault, S., Rochat, F., Brassart, D., Neeser, J.-R. and Servin, A.L., 2000. *Bifidobacterium* strains from resident infant human gastrointestinal microflora exert antimicrobial activity. Gut 47: 646-652.

Macedo, A., Banos, J.E. and Farre, M., 2008. Placebo response in the prophylaxis of migraine: A meta-analysis. European Journal of Pain 12: 68-75.

Mennigen, R. and Bruewer, M., 2009. Effect of probiotics on intestinal barrier function. Annals of the New York Academy of Sciences 1165: 183-189.

Miyauchi, E., O'Callaghan, J., Butto, L.F., Hurley, G., Melgar, S., Tanabe, S., Shanahan, F., Nally, K. and O'Toole, P.W., 2012. Mechanism of protection of transepithelial barrier function by *Lactobacillus salivarius*: strain-dependence and attenuation by bacteriocin production. American Journal of Physiology – Gastrointestinal and Liver Physiology 303: G1029-G1041.

Monteith, T. and Goadsby, P., 2011. Acute migraine therapy: new drugs and new approaches. Current Treatment Options in Neurology 13: 1-14.

Neeser, J.-R., Granato, D., Rouvet, M., Servin, A., Teneberg, S. and Karlsson, K.-A., 2000. *Lactobacillus johnsonii* La1 shares carbohydrate-binding specificities with several enteropathogenic bacteria. Glycobiology 10: 1193-1199.

Niers, L., Martin, R., Rijkers, G., Sengers, F., Timmerman, H., van Uden, N., Smidt, H., Kimpen, J. and Hoekstra, M., 2009. The effects of selected probiotic strains on the development of eczema (the PandA study). Allergy 64: 1349-1358.

Ohland, C.L. and Macnaughton, W.K., 2010. Probiotic bacteria and intestinal epithelial barrier function. American Journal of Physiology – Gastrointestinal and Liver Physiology 298: G807-819.

Parlesak, A., Schafer, C., Schutz, T., Bode, J.C. and Bode, C., 2000. Increased intestinal permeability to macromolecules and endotoxemia in patients with chronic alcohol abuse in different stages of alcohol-induced liver disease. Journal of Hepatology 32: 742-747.

Persborn, M., Gerritsen, J., Wallon, C., Carlsson, A., Akkermans, L.M. and Soderholm, J.D., 2013. The effects of probiotics on barrier function and mucosal pouch microbiota during maintenance treatment for severe pouchitis in patients with ulcerative colitis. Alimentary Pharmacology and Therapeutics 38: 772-783.

Pfaffenrath, V., Diener, H.C., Fischer, M., Friede, M., Henneicke-von Zepelin, H.H. and Investigators, 2002. The efficacy and safety of *Tanacetum parthenium* (feverfew) in migraine prophylaxis – a double-blind, multicentre, randomized placebo-controlled dose-response study. Cephalalgia 22: 523-532.

Piche, T., Barbara, G., Aubert, P., des Varannes, S.B., Dainese, R., Nano, J.L., Cremon, C., Stanghellini, V., De Giorgio, R., Galmiche, J.P. and Neunlist, M., 2009. Impaired intestinal barrier integrity in the colon of patients with irritable bowel syndrome: involvement of soluble mediators. Gut 58: 196-201.

Reid, G., Gaudier, E., Guarner, F., Huffnagle, G.B., Macklaim, J.M., Munoz, A.M., Martini, M., Ringel-Kulka, T., Sartor, B., Unal, R., Verbeke, K. and Walter, J., 2010. Responders and non-responders to probiotic interventions: how can we improve the odds? Gut Microbes 1: 200-204.

Salim, S.Y. and Soderholm, J.D., 2011. Importance of disrupted intestinal barrier in inflammatory bowel diseases. Inflammatory Bowel Diseases 17: 362-381.

Samsam, M., Covenas, R., Ahangari, R. and Yajeya, J., 2010. Neuropeptides and other chemical mediators, and the role of anti-inflammatory drugs in primary headaches. Anti-Inflammatory and Anti-Allergy Agents in Medicinal Chemistry 9: 170-188.

Scaldaferri, F., Pizzoferrato, M., Gerardi, V., Lopetuso, L. and Gasbarrini, A., 2012. The gut barrier: new acquisitions and therapeutic approaches. Journal of Clinical Gastroenterology 46 Suppl.: S12-17.

Schellenberg, R., Lichtenthal, A., Wohling, H., Graf, C. and Brixius, K., 2008. Nebivolol and metoprolol for treating migraine: an advance on beta-blocker treatment? Headache 48: 118-125.

Sensenig, J., Johnson, M. and Staverosky, T., 2001. Treatment of migraine with targeted nutrition focused on improved assimilation and elimination. Alternative Medicine Review 6: 488-494.

Shuhendler, A.J., Lee, S., Siu, M., Ondovcik, S., Lam, K., Alabdullatif, A., Zhang, X., Machado, M. and Einarson, T.R., 2009. Efficacy of botulinum toxin type A for the prophylaxis of episodic migraine headaches: a meta-analysis of randomized, double-blind, placebo-controlled trials. Pharmacotherapy 29: 784-791.

Stewart, W.F., Lipton, R.B., Whyte, J., Dowson, A., Kolodner, K., Liberman, J.N. and Sawyer, J., 1999. An international study to assess reliability of the Migraine Disability Assessment (MIDAS) score. Neurology 53: 988-994.

Van Hemert, S., Breedveld, A., Rovers, J., Vermeiden, J., Witteman, B., Smits, M. and de Roos, N., 2014. Migraine associated with gastrointestinal disorders: review of the literature and clinical implications. Frontiers in Neurology 5: 241.

Waeber, C. and Moskowitz, M.A., 2005. Migraine as an inflammatory disorder. Neurology 64: S9-15.

Wang, S.J., Chen, P.K. and Fuh, J.L., 2010. Comorbidities of migraine. Frontiers in Neurology 1: 16.

Wang, X., Shang, D., Ribbing, J., Ren, Y., Deng, C., Zhou, T., Guo, F. and Lu, W., 2012. Placebo effect model in asthma clinical studies: longitudinal meta-analysis of forced expiratory volume in 1 second. European Journal of Clinical Pharmacology 68: 1157-1166.