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'Brain Fogginess' and D-Lactic Acidosis: Probiotics Are Not the Cause

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In their recent study, Rao and colleagues[1] incriminated probiotics in the induction of D-lactic acidosis, thereby causing such symptoms as 'brain fogginess', abdominal pain, and bloating. This report has been picked up by dozens of media outlets—from Newsweek to Psychology Today—and has the potential to portray probiotics, products that are safely consumed by millions around the world, in a negative light. Many benefit from probiotics[2] and could be frightened—on the basis of this report—into stopping them, with potentially negative impacts on their health. For these reasons the study deserves careful scrutiny.

The problems with this paper are first signaled by the very title of the piece where the authors conflate two separate entities, probiotics and small intestinal bacterial overgrowth (SIBO), and, in so doing, give the impression that they are equally culpable in the pathogenesis of their patients' symptoms. No evidence is provided to support this.

- While the nature of the probiotic products consumed by these patients is not specified, it must be made clear that many lactobacilli and all bifidobacteria only produce L-lactate and do not possess the biochemical machinery to produce D-lactate[3]. Neither, for that matter, do bifidobacteria produce gases. The authors, in contrast, state that '**Both bacteria** (referring to *Lactobacillus* and *Bifidobacterium*) **produce D-lactic acid**' but provide no source for this statement.
- The authors go on to cite a paper by Gigante et al.[4] as evidence that probiotics can cause D-lactic acidosis. Our reading of this paper indicates that the only role that probiotics played in this case was in the successful treatment of the patient; they played absolutely no role in the genesis of symptoms of D-lactic acidosis.
- D-lactic acidosis is a serious condition typically reported in the setting of short bowel syndrome. In this context, the probiotic species *Lactobacillus johnsonii* and *Lactobacillus plantarum* were linked with D-lactic acidosis in a boy with short bowel syndrome but it was successfully treated with a probiotic cocktail containing non-D-lactate-producing probiotics[5]. Rao and colleagues fall into a common and treacherous trap—equating all probiotics. Their incrimination of 'probiotics' in this manner is sweeping and flagrantly misleading.
- It is also important to point out that, in contrast to cases reported in relation to short bowel syndrome where laboratory studies demonstrate actual acidosis and very high levels of D-lactate have been documented[6], Rao and colleagues do not provide any data to indicate that their patients were acidotic and the levels of D-lactate that they report were marginally above the upper limit of their normal range. At best, their paper describes D-lactic acidemia. Is there any evidence that such low levels of D-lactate are accompanied by any symptoms? As measurements of lactic acid levels in urine or blood were not repeated by Rao and colleagues following their interventions, the role of lactic acid in symptomatology must remain speculative.
- These patients were also diagnosed with SIBO—itself a contentious entity but one that has certainly been linked with D-lactic acidosis. It must be remembered that bacteria involved in SIBO can

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produce other metabolites, such as ethanol, that could, in theory, at least, lead to neuropsychiatric symptoms. In a condition as vague and ill defined as 'brain fogginess' great care must be exercised in attributing causality to any single factor.

- Probiotics were not the only therapies that were being consumed at the time of evaluation.
- Another important issue is that the patients' response to antibiotics and the cessation of probiotic consumption is far from conclusive on any front. First, this was not a randomized, double-blind study. Given the nature of the symptoms being addressed, the lack of any objective measures in follow-up, and the high placebo response rate associated with functional disorders, all symptom responses must be treated with caution. Second, multiple antibiotic regimens were employed. Studies in hepatic encephalopathy and elsewhere have revealed the complexity of antibiotic effects which may go well beyond quantitative changes in bacterial populations to the modulation of bacterial metabolism[7], or even anti-inflammatory effects[8]. Third, as the elimination of probiotics alone was not a strategy in the full study population, no conclusions can be drawn on the impact of probiotic withdrawal alone on symptom resolution. Fourth, even with regard to the role of SIBO, conclusions must be very guarded as the elimination of SIBO was not documented. The role of SIBO in functional syndromes is controversial; Posserud et al.[9], while failing to document an increased prevalence of SIBO in irritable bowel syndrome (IBS), as classically defined, did note what they referred to as 'mildly increased counts' of bacteria in their IBS subjects. Could this phenomenon be relevant to the population studied by Rao and colleagues and contribute to their response to antibiotics? Finally, these patients were on many other therapies and it is not clear which of these were continued or withdrawn following their evaluation.

Rao and colleagues are to be congratulated on attempting to find a solution to a symptom complex which was clearly so debilitating for these patients. This should not, however, preclude careful attention to trial design or permit unfounded extrapolations from findings which are limited in nature and problematic in so many aspects. The search for causes for these symptoms, be they bacteriological or otherwise, should go on but, in the meantime, it is critical that the public and their physicians not take alarm from conclusions regarding probiotics which are unfounded.

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References

1. Rao, S. S. C., Rehman, A., Yu, S. & Andino, N. M. Brain fogginess, gas and bloating: a link between SIBO, probiotics and metabolic acidosis. *Clin. Transl. Gastroenterol.* **9**, 162 (2018).
2. Sanders, M. E., Merenstein, D. & Merrifield, C. A. Probiotics for human use. *Nutr. Bull.* **43**, 212–225 (2018).
3. de Vries, W. & Stouthamer, A. H. Fermentation of glucose, lactose, galactose, mannitol, and xylose by bifidobacteria. *J. Bacteriol.* **96**, 472–478 (1968).
4. Gigante, A. et al. D-Lactic acidosis 25 years after bariatric surgery due to *Salmonella enteritidis*. *Nutrition* **28**, 108–111 (2012).
5. Yilmaz, B., Schibli, S., Macpherson, A. J. & Sokollik, C. D-lactic acidosis: successful suppression of D-lactate-producing *Lactobacillus* by probiotics. *Pediatrics* **142**, pii: e20180337 (2018).
6. Stanciu S., De Silva A. Metabolic acidosis in short bowel syndrome: think D-lactic acid acidosis. BMJ Case Rep. 2018;pii:bcr-2018-224221.
7. Kang, D. J. et al. Rifaximin exerts beneficial effects independent of its ability to alter microbiota composition. *Clin. Transl. Gastroenterol.* **7**, e187 (2016).
8. Sartor, R. B. Review article: the potential mechanisms of action of rifaximin in the management of inflammatory bowel diseases. *Aliment. Pharmacol. Ther.* **43** (Suppl. 1), 27–36 (2016).
9. Posserud, I., Stotzer, P. O., Björnsson, E. S., Abrahamsson, H. & Simrén, M. Small intestinal bacterial overgrowth in patients with irritable bowel syndrome. *Gut* **56**, 802–808 (2007).