



## Commentary

## Quo Vadis, Probiotics? Human Research Supports Further Study of Beneficial Microbes in Mental Health



Martin A. Katzman <sup>a,b,c,d,e,f,\*</sup>, Alan C. Logan <sup>g</sup>

<sup>a</sup> Clinic Director, Stress Trauma Anxiety Rehabilitation and Treatment (START) Clinic for Mood and Anxiety Disorders, 32 Park Road, Toronto, ON M4W 2N4, Canada

<sup>b</sup> Department of Psychiatry, Northern Ontario School of Medicine, Canada

<sup>c</sup> Department of Psychology, Adler Graduate Professional School, Canada

<sup>d</sup> Department of Psychology, Lakehead University, Canada

<sup>e</sup> Chair, Scientific Advisory Board, Anxiety Disorders Association of Canada/Association (ADAC/ACTA), Canada

<sup>f</sup> Treasurer, American Professional Society of ADHD and Related Disorders (APSARD), United States

<sup>g</sup> FLAME Global Network, Research Group of the Worldwide Universities Network (WUN), 6010 Park Ave, Suite #4081, West New York, NJ 07093, United States

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*“The cases have been too few in number and the treatment has been carried out for too short a time to warrant me in making any generalization, and my sole object is to suggest that this method of treatment may be given a trial”* Hubert J. Norman, MD (1909)

Writing in the *British Medical Journal* in 1909, Dr. Hubert Norman described some modest benefits in the treatment of melancholia with a novel intervention - lactic acid bacilli. Careful with his words, Norman was urging colleagues to engage in more thorough study of his observations. However, other than some further case reports, the application of lactobacilli-fermented milk and tablets to improve mood became a commercial, rather than a scientific, enterprise (Bested et al., 2013).

Without plausible scientific mechanisms, the idea that gut microbiota (or targeted use of microbial products) could ‘manipulate’ mental health would always seem implausible. More than a century later, researchers are revisiting these ideas with the aid of scientific advances that were undreamt of in the time of Norman. New methods of microbial identification in concert with metabolomics and other ‘omics’ ad-

vances are providing greater precision in the quest to link microbial forms with everyday function.

Clever studies using germ-free animal models have proven that gut microbes make an essential contribution to mammalian brain chemistry (Hegstrand and Hine, 1986). Animal studies have demonstrated gut microbe-to-brain communication via the vagus nerve. Manipulation of the animal microbiota with antibiotics, westernized diet, stress and various “lifestyle” factors can result in altered behavior reflective of human anxiety and depression; a causative role for microbiota is hinted at through fecal transfer studies wherein behavioral and metabolic alterations are carried with the microbiota. Studies have linked the bi-directional relationship between the immune system and microbiota - most notably through cytokine response to systemic endotoxin - to brain function and behavior (Koopman and El Aidy, 2017). Two-way links between gut microbiota and specific aspects of dietary patterns (e.g. omega-3 fatty acids, polyphenols) and antioxidant status are also relevant to depression.

The slow and steady build-up of pre-clinical research in the last two decades has now set the table for what Norman was seeking - human research. Although there have been some recent human studies examining beneficial microbes in the realm of general mental well-being, or mental health associated with various disorders and syndromes, collectively the body of human data remains tissue-paper thin. Thus far, the human research has largely involved small sample sizes and pilot studies to determine if the elegant, if not astonishing, pre-clinical findings might translate to humans (Wallace and Milev, 2017).

In this issue of *EBioMedicine*, Slykerman et al. advance the case for more urgent study of the use of beneficial microbes in the realm of mental health (Slykerman et al., 2017). Specifically, they evaluated whether the application of a probiotic (*Lactobacillus rhamnosus* HN001, 6 billion cfu daily; initiated during the 2nd trimester through 6 months postpartum) might influence the symptoms of depression and/or anxiety in the postpartum period. With a randomized, double-blind, placebo-controlled design, a well-defined probiotic strain, and a large sample size ( $n = 380$  completed), the study of Slykerman et al. represents the first large-scale effort toward translation. The results are certainly encouraging; women in the probiotic group reported significantly lower

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\* Corresponding author at: Stress Trauma Anxiety Rehabilitation and Treatment (START) Clinic for Mood and Anxiety Disorders, 32 Park Road, Toronto, ON, M4W 2N4, Canada.

E-mail addresses: [mkatzman@startclinic.ca](mailto:mkatzman@startclinic.ca) (M.A. Katzman), [aclnld@cfs-fm.org](mailto:aclnld@cfs-fm.org) (A.C. Logan).

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depression scores and anxiety scores based on slightly amended versions of the Edinburgh Postnatal Depression Scale (EPDS) and State Trait Anxiety Inventory (STAI-6). Indeed, using a cut-off score > 15 as an indicator of clinical significance on the STAI-6, the reduced anxiety in the probiotic group (vs. placebo) may have clinical relevance.

The new study is not without limitations; reliance upon retrospective measurement (the EPDS and STAI-6 questions were amended to past-tense) is the most significant impediment to translation value. Moreover, the study did not evaluate the use of a probiotic in the prevention and/or treatment of any diagnosed psychiatric disorder, postpartum depression or otherwise. The study outcomes - secondary to the primary endpoints of eczema and atopic sensitization - were directed at symptomatology; put simply, a large, well-designed, controlled trial of probiotics in postpartum depression awaits.

There are many different roads to take in the journey toward clinical translation of voluminous pre-clinical gut-brain-microbiota data. Given the suffering and long-term health consequences of postpartum depression, including neuropsychiatric problems in offspring (O'Connor et al., 2016), the argument to direct resources toward the developmental origins of health and disease (DOHaD) is strong. Indeed, early-life exposure to specific beneficial microbes is emerging as a critical area of research in the general effort to curb non-communicable diseases - an epidemic of which mental disorders are one, related part.

Slykerman et al. are to be commended for taking initial steps to evaluate the application of probiotics in mental health; wisely, they underscored the need for replication studies before *Lactobacillus rhamnosus* HN001 (or any other probiotic) can be considered useful for the prevention or treatment of symptoms of depression and anxiety postpartum. Depression is a serious, complex, potentially-life threatening illness which is more likely to occur along the lines of socioeconomic disadvantage; it would be a tall order to expect probiotics to be anything other than adjuvant treatment (Logan and Katzman, 2005). While new, scientifically-plausible, treatment options are welcome, the illness is not served well by headlines such “Forget Prozac, Psychobiotics are the Future of Psychiatry” (Tetro, 2013). Major depression isn't the common cold or a mild upper respiratory tract infection; overselling probiotics (or so-called “psychobiotics”, a name which might contribute to stigma (Wallace and Milev, 2017)) for mental disorder at the expense of

standard, evidence-based care is reckless. Even with the addition of the compelling new research of Slykerman et al., Norman's 1909 caution remains: The cases are still too few in number, no generalizations can be made, and the new research should be interpreted only as a stimulus that “the method” warrants further study.

### Competing Interests

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