The gut-brain axis in personalised mental healthcare

Introduction

Considerable new research into the microbiome of the human gastrointestinal tract is focusing firstly on the changes in the microbiota over our lifespan from infancy,¹ and secondly on the links between the gastrointestinal microbiota and the central nervous system (CNS).² This review seeks to update the busy clinician on probiotics and the newer concept of ‘psychobiotics’, known probiotics that have shown beneficial effects in alleviating symptoms of mental ill health. This is important for the clinician, as patients with immune or common neurological conditions read more about their condition and seek advice on the value of probiotics and dietary modification of their symptoms.

Data are presented on:

• Mechanisms of communication between gut and brain
• Current understanding of microbiota in early life and the value of therapy in infants and children
• The critical differences in the microbiota of people with depression, schizophrenia and cognitive frailty
• The potential benefits of probiotic consumption on the immune system, the maintenance of a healthy microbiome, the alleviation of symptoms of depression and anxiety, and improvement of neurocognitive performance.
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**KEY MESSAGES**

- Improved understanding of the gut-brain axis is identifying new pathways for treating depression
- The increased patient preference for complementary and alternative medication for common neurological conditions demands an informed response from clinicians
- The use of probiotics as an adjuvant to the treatment of mild/uncomplicated depression is worth considering in some patients.

**Mechanism of gut microbiota-brain communication**

This is an evolving area of research, but currently the major areas of focus are immune signals and the vagus nerve. Cellular components such as lipopolysaccharides, peptidoglycan and flagellin are recognised by so-called pattern recognition receptors (Toll-like receptors, for example) on epithelial and immune cells. This leads to the production of cytokines, hormones and other molecular signals, which act as neurotransmitters within the CNS (Figure 1). Alterations in microbiota can also alter the excitability of enteric nervous system neurons and influence the vagus nerve, which is involved in bidirectional communication.

The central part of the figure shows the bidirectional influence between the brain and gut microbiota. The left side shows modes of communication in the bidirectional crosstalk between gut microbiota and the brain and the possible influences of prebiotics and probiotics on human diseases. The right side of the figure shows the consequences of gut dysbiosis/homeostasis. Intestinal dysbiosis can adversely influence gut physiology, leading to inappropriate brain-gut axis signalling and associated consequences for CNS functions and disease states.

**Homeostasis:**
- Normal functioning of the immune system
- No gut inflammation
- Normal gut motility
- Nutrient assimilation
- Normal long-term cognition, behaviour and neurodevelopment

**Probiotics:**
- Improvement of a variety of human diseases (NAFLD, allergic diseases, asthma, atopic disease)
- Antibiotic therapy reduction
- Improvement of immune-related diseases (IBD, coeliac disease, metabolic syndrome, diabetes)
- Beneficial health benefits (anxiety, depression and eating behaviour regulation and gut pain reductions)

**Prebiotics:**
- Support probiotic growth/activity

**Dysbiosis:**
- Neurological disorders (depression, anxiety, ADHD, ASD)
- Autoimmune disorders (IBD, Crohn’s disease, coeliac disease, allergies)
- Metabolic syndrome (obesity, type 2 diabetes, hypercholesterolaemia, hypertension)

**Abbreviations:** Non-alcoholic fatty liver disease (NAFLD), inflammatory bowel disease (IBD), attention deficit hyperactivity disorder (ADHD), autism spectrum disorder (ASD).
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Microbiota in early life

While the process of establishing the very first bacterial communities in the gut is not well understood, three environmental factors influence the early maturing of the microbial ecosystem:
1. Mother-to-child bacterial transfer
2. Method of delivery (vaginal or caesarean)
3. Type of feeding.

In turn, changes in the gut microbiota in these first few years may influence this period of rapid brain development. It is for these reasons that prenatal and postnatal maternal oral probiotic therapy may represent an opportunity to ensure better physical and neurodevelopment of the foetus and young infant (up to three years).²

Critical differences in microbiota in depression, cognitive frailty and schizophrenia

Research into the gut microbiota has progressed as a result of improvements in microbiological testing. It is now possible to obtain a complete genetic breakdown of a person’s gut microbiota in one day.³ This has resulted in an explosion of information about the gut microbiome in health and disease.

In schizophrenia patients, an investigation of the gut microbiome composition, as compared to non-psychiatric patients, has shown significant differences.⁴ Similarly, in major depressive disorder, significant differences in taxa were observed when compared to healthy controls.⁵

In studies of older individuals with physical frailty, mobility limitations and multiple morbidities (e.g. cardiac dysfunction, sarcopenia, insulin resistance), microbiota have a much lower diversity of taxa.⁶,⁷

Benefits and potential benefits of probiotics

The value of probiotics in reducing diarrhoea associated with antibiotics is well documented. Also probiotics have been shown to reduce symptom severity in immune-related diseases such as IBD, coeliac disease, metabolic syndrome and diabetes.

The search for psychobiotics that can affect cognitive function has increased in recent years. Some positive results have been shown with regard to maternal depression and anxiety in the postpartum period, as well as depression in irritable bowel disease.

Alleviating anxiety and depression postpartum

A double-blind study was undertaken in which the effect of giving a probiotic (Lactobacillus rhamnosus HN001) was assessed primarily for its effect on eczema in the offspring, but with a secondary outcome assessing symptoms of maternal anxiety and depression.⁸ Four hundred and twenty-three women were included in the study and randomised to either the probiotic or placebo. Mothers in the probiotic treatment group reported significantly lower depression scores (effect size -1.2, 95% CI -2.3, -0.1) and anxiety scores (effect size -1.0, 95% CI -1.9 - 0.2). Rates of clinically relevant anxiety on screening (score <15 as measured by the Edinburgh Postnatal Depression Scale) were significantly lower in the treated mothers (OR=0.44, 95% CI 0.26, 0.73, p=0.002).

Alleviating depression in irritable bowel syndrome

In a randomised, double-blind, placebo-controlled study of adults with irritable bowel syndrome and mild-to-moderate anxiety and/or depression, Bifidobacterium longum (NCC 3001 (BL)) was given for six weeks and its effect assessed on brain activation patterns, faecal microbiota and serum markers of inflammation, neurotransmitters and neurotrophin levels.⁹ The functional magnetic resonance imaging analysis showed that BL reduced responses to negative

“*The microbiome of infants is clearly far more complex than originally anticipated.*”
Professor Dicks
emotional stimuli in multiple brain areas, reducing depression scores but not anxiety scores. Importantly, these improvements were associated with changes in brain activation patterns indicating reduced limbic reactivity. This is a pilot study (44 patients) and a larger study is currently underway.

**Conclusion**

The interest in the gut-brain axis and the benefits of probiotics in alleviating depression, anxiety and improving neurocognitive performance is likely to grow, with significant clinical opportunities emerging in the future.

**References**