Pathways underlying the potential effect of Lactobacillus helveticus in major depression: a randomized, double-blind, placebo-controlled, add-on trial

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What is the Methodological Question Being Addressed? Do changes in gut microbiota and inflammatory biomarkers mediate the effects of an add-on treatment with a probiotic (Lactobacillus helveticus) on depressive symptoms?

Introduction There is a growing interest in studying the bidirectional interaction between the brain and the gut, named the 'brain-gut-microbiome axis. Pre-clinical studies showed that antidepressants affect the gut microbiota, influencing the rate of responsiveness to the treatment. In parallel, the use of probiotics is a strategy for manipulating the gut microbiota and can lead to mood improvement. Therefore, we hypothesized that the treatment with antidepressants concomitantly with a probiotic [Lactobacillus helveticus (L. helveticus)] could modify the gut microbiota and modulate inflammatory pathways, which mediate the improvement of depressive symptoms. The overall aim of this study is to investigate the pathways underlying the potential antidepressant effect of L. helveticus as an add-on strategy in the treatment of MDD. Our first aim is to assess whether adding L. helveticus to standard antidepressant treatment changes the gut microbiota and inflammatory biomarkers serum levels in patients with MDD. Our second aim is to evaluate what gut microbiota signatures and inflammatory biomarkers are associated with depressive symptoms improvement.

Methods We will analyze the clinical results and samples of an ongoing randomized, double-blind, placebo-controlled add-on clinical trial (NCT04333277). Forty-two (n=42) patients with Major Depressive Disorder were divided into two groups (ratio 1:1): One group is receiving one dose a day of probiotic [L. helveticus (10^9 CFU/day)] and another group is receiving the same amount of placebo (maltodextrin) for eight weeks. All patients receive an adequate prescription (antidepressant) plus the probiotic or placebo. The patients are evaluated at baseline, four weeks, and eight weeks after the treatment onset. Symptoms of depression, anxiety, and stress are measured at each visit using the Montgomery-Åsberg Depression Scale, Hospital Anxiety and Depression Scales, and Perceived Stress Scale. Blood and stool samples are collected at all visits. We will measure a comprehensive panel of 20 peripheral inflammatory biomarkers by Elisa and Luminex: Adiponectin, Leptin, Resistin, Insulin-like growth factor-binding protein-1, Tumor Necrosis Factor (TNF), sTNFR1, sTNFR2, TNF-like weak inducer of apoptosis, Interleukin (IL)-1β, IL-2, IL-4,

IL-6, IL-6R, IL-8, IL-10, IL-13, IL-15, IL-18, IL-33, and ST-2. The gut microbiome composition will be characterized using whole-genome shotgun sequencing of DNA extracted from the stool samples.

Results Forty-two patients were already enrolled in the study. Most participants were women (88.1%) and the median age was 46 (18-62) years old. The baseline mean score ± standard deviation of Montgomery-Åsberg Depression Scale, Hospital Anxiety and Depression Scales, and Perceived Stress Scale were 23.0 ± 6.7, 12.9 ± 3.7, 11.8 ± 3.5, and 30.7 ± 4.8, respectively. Most patients are taking serotonin reuptake inhibitors (SSRIs) (66.6%) and serotonin and norepinephrine reuptake inhibitors (SNRIs) (30.9%).

Conclusion This study will shed light on the mechanisms underlying the effects of probiotics on mood. Furthermore, if our hypothesis is confirmed, this study will pave the way for identifying and using specific microbial strains in the treatment of MDD.

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