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

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METHODOLOGICAL QUESTION:

Do changes in the gut microbiota and inflammatory biomarkers mediate the effects of an adjuvant treatment with a probiotic (*Lactobacillus helveticus*) in 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** (1).
- Pre-clinical studies showed that antidepressants affect the gut microbiota, influencing the rate of responsiveness to the treatment (1, 2).
- In parallel, the use of probiotics is a strategy for manipulating the gut microbiota and can lead to mood improvement (3, 4).

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.

OBJECTIVES:

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:

- **Design**: Randomized, double-blind, placebo-controlled add-on clinical trial (NCT04333277).
- **Patients' enrollment**:

Inclusion Criteria: **(i)** Aged between 18 and 65 years old; **(ii)** Diagnosis of MDD (according to DSM-V criteria).

Exclusion Criteria: **(i)** Treatment with psychotropic, anti-inflammatory or antibiotics of any pharmacological classes in the month before treatment enrollment; **(ii)** Use of dietary supplementation (herbal supplements, other pro- or prebiotics).

- **Sample size:** 20 participants per group
- **Treatment:**

Probiotic *(L. helveticus* - 10^9 CFU/day)

OR

Placebo (Maltodextrin powder)

*All patients received antidepressants prescribed according to individual needs.

- *Treatment duration:* 8 weeks

*The patients were evaluated at baseline (T1), week 4 (T2), and week 8 (T3) of the treatment.

- *Biological samples:* Blood and stool samples were collected at all three time points.
- *Clinical measures*: The Montgomery-Åsberg Depression Scale (MADRS), the Hospital Anxiety and Depression Scale (HADS) and Perceived Stress Scale (PSS).
- **Location**: Instituto de Previdência dos Servidores do Estado de Minas Gerais (IPSEMG) in Belo Horizonte, Minas Gerais, Brazil.
- **Analytical plans**: Blood biomarkers (ELISA and Luminex) and gut microbiota characteristics (Shotgun technique).

RESULTS:

- Forty-two patients were already enrolled in the study (20 received placebo and 22 probiotic).
- Most participants were women (88.1%) and the median age was 46 (18-62) years old.
- There was no difference between the Placebo and Probiotic group in the demographic and clinical aspects.
- The baseline mean score ± standard deviation of MADRS, HADS-A, HADS-D and PSS were 23.0 ± 6.7, 12.9 ± 3.7, 11.8 ± 3.5, and 30.7 ± 4.8, respectively.
- Most patients was taking serotonin reuptake inhibitors (SSRIs) (66.6%) and serotonin and norepinephrine reuptake inhibitors (SNRIs) (30.9%).
- ***Preliminary data:***

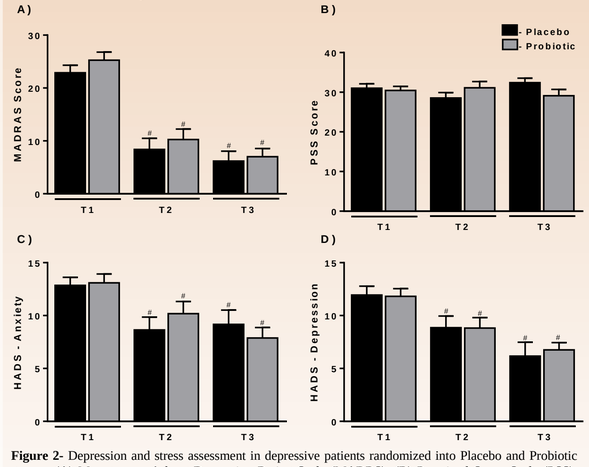

Figure 2- Depression and stress assessment in depressive patients randomized into Placebo and Probiotic groups. (A) Montgomery-Asberg Depression Rating Scale (MADRS); (B) Perceived Stress Scale (PSS); (C) Hospital Anxiety and Depression Scale for the anxiety severity symptoms (HADS-Anxiety); (D) Hospital Anxiety and Depression Scale for the depression severity symptoms (HADS-Anxiety).
Significant differences were considered when $p < 0.05$
#Difference when compared to T1 (baseline)
(Kruskal-Wallis test to compare Placebo x Probiotic in the different time points; and Wilcoxon test for the three-time points in the same group).

- No difference between the placebo and probiotic groups was found at any time point.
- ***Treatment Response:***

MADRAS		**Week 4**	**Week 8**
Responders (↓≥ 50%)	Placebo	13	16
	Probiotic	13	17
	Total	*26*	*33*
Non-responders	Placebo	7	4
	Probiotic	9	5
	Total	*16*	*9*

PERSPECTIVES:

- *Further questions to be address:*

Does antidepressant use change gut microbiota and inflammatory markers?

Does the use of probiotics as an adjunct to antidepressant treatment change the composition of the microbiota and influence the levels of serum inflammatory markers?

Are there specific microbial signatures associated with responsiveness to depressive treatment?

CONCLUSION:

These results suggest that the antidepressant treatment was effective for both groups, but the coadjutant treatment with probiotic was not different from placebo. However, it is still unclear whether the composition of the microbiota can influence the antidepressant treatment response.

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DISCLOSURES:

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