STUDY PROTOCOL

Official Study Title

Effect of Psychobiotics Combined with Standard Antidepressant Therapy in the Treatment of Major Depressive Disorder: A Randomized Controlled Trial

Clinical Trial Information

NCT Number: NCT07691749

Protocol Number: ERB 198/06/01-01-2026/AIMC/JHL

Document Date: 11th February 2026

Sponsor

Department of Psychiatry & Behavioural Sciences

Allama Iqbal Medical College / Jinnah Hospital, Lahore, Pakistan

Introduction:

Depression remains one of the most pervasive mental health disorders globally, contributing massively to disability and impaired functioning. Recent data from the Global Burden of Disease (GBD 2021) estimate that over **330 million people** worldwide suffer from depressive disorders, accounting for approximately **56 million disability-adjusted life years (DALYs)**. The burden of depression increased substantially during and after the COVID-19 pandemic, with studies from 2020–2022 reporting an **11–28% rise** in depressive symptoms, particularly in socially vulnerable populations[(1),(2,3)].Young adults, adolescents, and women of reproductive age are among those most affected, experiencing sharp increases in prevalence and severity [(4)] .

In Pakistan, the public health impact of depression is similarly alarming. National burden data suggest that depressive disorders represent around **3.1% of Pakistan's total DALYs**, with female populations disproportionately affected [(4)]. According to the National Psychiatric Morbidity Survey (2022–2024), **19–22% of Pakistani adults** report mood disorders, including depression[(5)]. Urban and high-risk groups—including medical students, those with chronic illness, and underserved communities—show prevalence rates between **40% and 57%** in recent cross-sectional studies [(6)] [(7)]. Notably, psychological distress surged during the COVID-19 lockdown, with a national survey reporting nearly **40% prevalence** of depressive symptoms [(8)]

Given the limitations of conventional antidepressant therapies such as delayed onset, incomplete response, and adverse effects, novel adjunctive strategies are needed. One highly promising avenue is the **microbiota-gut-brain axis**, which mediates bidirectional communication between the gut microbiome and central nervous system function. **Psychobiotics**—live microorganisms that confer psychiatry-relevant benefits—are emerging as potential adjuncts for mood disorders.

Two psychobiotic strains, *Lactobacillus helveticus* and *Bifidobacterium longum*, have garnered significant scientific interest due to their neuroactive properties:

- **Lactobacillus helveticus** has been shown to modulate the hypothalamic-pituitary-adrenal (HPA) axis, reduce cortisol, support GABAergic signaling, and strengthen intestinal barrier function, thereby reducing systemic and neuroinflammation.
- **Bifidobacterium longum** acts via immunomodulation (decreasing pro-inflammatory cytokines), promoting serotonin synthesis, and engaging the vagus nerve, which collectively promote stress resilience and mood stabilization.

When used in combination, *L. helveticus* and *B. longum* have demonstrated **synergistic effects**, enhancing emotional processing, reducing physiological stress markers, and improving stress response, as shown in randomized controlled trials and functional neuroimaging studies.

Importantly, Pakistani researchers are contributing to this growing field. A systematic review from Pakistani scientists (Hussain et al., 2025) highlights the promise of psychobiotics, including *L. helveticus* and *B. longum*, in mental health[(9)]. Additionally, a narrative review by Imran et al. (2023), based in Pakistan, outlines how these strains may regulate neurotransmitters (like serotonin and dopamine), modulate immune responses, and mitigate inflammation via the gut–brain axis in depression [(10)]. Local probiotic research has also identified *L. helveticus* isolates in traditional Pakistani yogurt, providing a foundational base for future psychobiotic studies in the national context [(11)].

Given this background, the aim of this synopsis is to evaluate the effect of combining psychobiotic supplementation (L. helveticus + B. longum) with standard antidepressant therapy in depressive disorders, leveraging evidence from both international and Pakistani research (2020–2025).

Hypothesis
Adjunctive supplementation of *L. helveticus* and *B. longum* with standard antidepressants will significantly reduce depressive symptoms compared to standard antidepressants alone in adults with major depressive disorder (MDD).

Objective

To evaluate the degree of effectiveness of adjunctive psychobiotics (combined Lactobacillus helveticus + Bifidobacterium longum) compared with placebo, when given alongside standard antidepressant treatment, in reducing depressive symptoms measured by the HDRS-17 total score at 3 and 6 weeks in adults with Major Depressive Disorder (MDD).

Operational Definitions:

1. **Major depressive disorder:** Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure. Note: Do not include symptoms that are clearly attributable to another medical condition. [(12)]

    - Depressed most of the day, nearly every day as indicated by subjective report (or observation made by others).
    - Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by subjective account or observation).
    - Significant weight loss when not dieting or weight gain (e.g., change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day

- Insomnia or hypersomnia nearly every day.
- Psychomotor agitation or retardation nearly every day.
- Fatigue or loss of energy nearly every day
- Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick).
- Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others).
- Recurrent thoughts of death, recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.

The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning and are not attributable to the physiological effects of a substance or another medical condition. The episode meets criteria for a major depressive episode and is not better explained by schizoaffective disorder, schizophrenia, or other psychotic disorders. There is no history of manic or hypomanic episodes.

2. Psychobiotics: Capsular form of psychobiotics i-e live microorganisms specifically blended with two live bacterial strains Lactobacillus ***helveticus*** R0052 -1.8 billion CFUs (Colony Forming Units) and Bifidobacterium ***longum*** R0175- 1.2 billion CFU.

3. Placebo capsule:
A placebo capsule is an orally administered capsule formulated with inert gelatin and no active ingredients. It has no psychobiotic potential and is pharmacologically inactive. The capsule is not expected to affect study outcomes or interact with oral selective serotonin reuptake inhibitors (SSRIs)

3. Standard Antidepressants Treatment: Patients taking stable dose of oral selective serotonin reuptake inhibitors for at least 2 weeks prior to enrollment in study.

4. Effectiveness: Intervention will be labeled as effective if after six weeks of psychobiotics use, the cut off value of Hamilton depression rating scale {< 24} has been reduced.

Methodology

Study Design:
Randomized, double-blind, placebo-controlled clinical trial.

Study Duration:

The study will conduct within three months after approval of synopsis from Institutional Review Board/ Ethical Review Committee of Allama Iqbal Medical College.

Place of study:

Study will be conducted in the Department of Psychiatry, Jinnah Hospital, Lahore.

Sample Size Calculation:

The sample size was calculated by using PASS 2021 Software.

Group sample sizes of 34 and 34 achieve 90.15% power to reject the null hypothesis of zero effect size when the population effect size is 0.8 and the significance level (alpha) is 0.05 using a two-sided two-sample equal-variance t-test.

Reference [13]

Cohen, Jacob. 1988. Statistical Power Analysis for the Behavioral Sciences. Lawrence Erlbaum Associates. Hillsdale, New Jersey Julious, S. A. 2010. Sample Sizes for Clinical Trials. Chapman & Hall/CRC. Boca Raton, FL.
Machin, D., Campbell, M., Tan, B. T., Tan, S. H. 2009. Sample Size Tables for Clinical Studies, 3rd Edition.[14]

Keeping in view the 20% expected dropout rate 43 subjects will be enrolled in intervention group and 43 subjects will be enrolled in control group.

Group Allocation:

This will be done through block randomization using online software.[15] Block size will be kept six. Unique randomization code (unique ID) will be allotted to each participant of the study.

Inclusion criteria:

- Patients diagnosed with major depressive disorder (According to Diagnostic & Statistical Manual-5 criteria (as per operational definition)
- Age 18 to 60 years
- Both genders
- Patients who are able to speak and understand Urdu/ English language.
- Patients who are on stable doses of oral selective serotonin reuptake inhibitors for at least two weeks prior to enrollment in the study
- Patients with cut off score of $\geq$ 24 as assessed by 17 item clinician administered Hamilton depression rating scale.

Exclusion Criteria:

- Severe psychiatric comorbidities (schizophrenia, bipolar disorder, co morbid substance use)
- Individuals with weakened immune systems: This includes patients undergoing chemotherapy, transplant recipients, and people with conditions like HIV/AIDS.
- Individuals on chronic medication: People on chronic pharmacological therapy, especially with anti-inflammatory drugs or who have recently used antibiotics in last 2 weeks.
- Pregnant or lactating women
- Current use of probiotics or prebiotics

STATISTICAL ANALYSIS PLAN

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Data Collection Procedure and Detailed Methodology:

After taking approval from the Institutional Review Board and Ethical Review Board, Allama Iqbal Medical College, eighty-six patients in total who fulfill the criteria of inclusion will be enrolled in the study. Written informed consent will be taken from all the patients. Demographic details, detailed clinical history will be taken from all the patients and findings will be noted down on a predesigned proforma. Hamilton depression rating scale scores will be noted down at the baseline by the principal investigator herself. Patients will be then categorized by co-investigator-1 into two equal groups (1:1 allocation) using **randomized block technique i.e. 43 patients in each group**. Concealment will also be done by co-investigator-1 using sequentially numbered (unique ID), sealed and stapled envelopes containing details of the allocated group. Patients in group A (interventional group) will be given psychobiotic capsules (once daily dose to be taken after breakfast) in addition to already prescribed treatment. Capsules will be provided by co-investigator-2, every week for consecutive six weeks. Patients in group B (control group) will receive antidepressant treatment as standard of care. Placebo capsules will be given by co-investigator 2 to patients of control group following the same schedule and procedure that was opted for group A.

Follow Up Procedure:

At the end of three and six weeks, the principal investigator will apply HDRS, scores will be noted down on the proformas and findings will be subjected to statistical analysis. During the entire study period, if any participant needed any non-financial help or assistance, it will be provided to him/her. Participants in the intervention group will be monitored for potential side effects associated with *Lactobacillus Helveticas* and *Bifidobacterium longum*, including bloating, abdominal discomfort, nausea, constipation, diarrhea, and headache. Any rare but clinically important adverse effects, such as signs of infection in vulnerable individuals, will also be assessed. All adverse effects will be recorded at each follow-up visit. If any side effect becomes **persistently distressing**, **clinically significant**, or if the participant expresses inability to

continue, the participant will be **withdrawn from the study** for safety reasons, and appropriate medical care will be ensured. Any participant whose SSRI dose needs to be increased or decreased, or for whom an adjunct antipsychotic or mood stabilizer needs to be added, will be withdrawn from the study.

If intervention is found to be effective, the patients in control group (group B) will be provided psychobiotics capsules for consecutive six weeks (similar schedule that was opted for intervention group), after the completion of study.

Ethical Considerations:

All procedures will adhere to established ethical guidelines for clinical research, including prior approval from the institutional ethics review board. Participants will be informed of their right to withdraw at any stage without penalty. Potential risks and benefits will be clearly explained, and efforts will be made to minimize any discomfort. Data integrity will be ensured through standardized protocols, and monitoring for adverse events will be conducted throughout the trial. No financial or coercive incentives will be offered, and the study will comply with all relevant regulatory and reporting requirements**.**

Conflict of Interest:

Genetics Pharmaceuticals will provide the psychobiotic capsules and placebo capsules to the principal investigator for use in the study. The company will not provide any financial assistance to the participants or the research team. Furthermore, Genetics Pharmaceuticals will not be involved in the study design, data collection, data analysis, interpretation of results, or manuscript preparation. The research team will retain full independence in conducting and reporting the study.

Data Analysis Procedure:

Data will be entered and analyzed using SPSS-25. Quantitative data such as age, HDRS score, duration of illness and effectiveness of intervention will be presented as mean and standard deviation. Qualitative data such as gender will be presented as frequency and percentages. Data will be stratified for age, gender and duration of illness. Post-stratification chi square test will be applied to deal with effect modifiers and a p-value of ≤ 0.05 will be considered as significant. Effectiveness of both interventions will be compared by independent t-test and a p value of ≤ 0.05 indicates a difference in effectiveness between both groups. For calculating the effect size of independent samples T-test, Cohen's d will be determined by calculating the mean difference between two groups, and then dividing the result by the pooled standard deviation.

References:

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15. Create a blocked randomisation list | Sealed Envelope [Internet]. [cited 2025 Nov 25]. Available from: https://www.sealedenvelope.com/simple-randomiser/v1/lists

INFORMED CONSENT

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CONSENT FORM

Title of Study: - Effect of psychobiotics (combined lactobacillus helveticus and bifidobacterium longum) with standard antidepressant treatment in major depressive disorder.
Institute: - Jinnah hospital, Lahore.
Aim of Study: - The aim of this study is to determine the effectiveness of psychobiotics in reducing the depression severity among patients with major depressive disorder.
Method: - After getting "Informed Consent", socio-demographic and clinical data, patients will be divided into two groups. One group will take daily dose of psychobiotics capsules for 6 consecutive weeks in addition to already prescribed treatment and other will get treatment as standard of care with placebo capsules. Hamilton depression rating scale score will be administered at baseline and after 3 and 6 weeks to both groups to see effectiveness of intervention.
Benefit of Study: - The current study will help in deciding whether or not psychobiotics which if implemented earlier can reduce the depression severity and that can further help in reducing overall morbidity that is associated with this condition and improving overall quality of life of patients.
Possible Risks: - There is no harm to the patients participating in this study. Minor side effects, if persistently reported will be addressed.
Confidentiality: - Names, contact information or any other personal information of the patients will be held in strict confidentiality. The results will be reported in aggregate form only, and will not be identified individually.

For further Details about the Information:

You can contact with the principal investigator regarding this research at any time.

Name: - Dr Sadia Yasir **Contact:** 03314567690

Undertaking: -

I have thoroughly read the consent form and fully understood it. I volunteer to participate in the research and if in future any follow up treatment is required, then I will be given that according to the standard of care.

(Name of participant) **Date:-**

Patient Information Leaflet

Study Title:

Effect of Psychobiotics (Lactobacillus helveticus + Bifidobacterium longum) with Standard Antidepressant Treatment in Major Depressive Disorder

Principal Investigator:

Dr. Sadia Yasir

Department of Psychiatry, Jinnah Hospital Lahore

Phone: 0331-4567690

1. Purpose of the Study

This study aims to determine whether adding psychobiotics to standard antidepressant medication can reduce depressive symptoms more effectively.

2. Why Am I Being Invited?

You are being invited because:

- You are 18–40 years old
- You have Major Depressive Disorder
- You have been taking antidepressants for at least 2 weeks
- Your HDRS-17 score is >24
- You understand Urdu or English

3. What Will Happen If I Take Part?

If you agree:

1. Your clinical and demographic data will be recorded.
2. You will be randomly allocated to:

Group A: Psychobiotics + antidepressant

Group B: Placebo + antidepressant

3. You will take one capsule daily for 6 weeks.

4. Your depression score will be measured at baseline, week 3, and week 6.

5. Weekly follow-ups will record symptoms and side effects.

4. Duration

Your participation will last 6 weeks.

5. Risks and Side Effects

Possible mild effects:

- Bloating

- Nausea

- Constipation or diarrhea

- Headache

6. Benefits

You may experience improvement; results may help future patients.

7. Confidentiality

Your identity will remain confidential.

8. Voluntary Participation

You may withdraw anytime without

affecting your treatment.

9. Cost

Participation is free of cost.

Contact Details

Dr. Sadia Yasir

Department of Psychiatry, Jinnah Hospital Lahore
0331-4567690

SOCIODEMOGRAPHIC AND CLINICAL DATA (TO BE FILLED BY PRINCIPAL INVESTIGATOR)

Study Title: Effect of psychobiotics (combined lactobacillus helveticus and bifidobacterium longum) with standard antidepressant treatment in major depressive disorder.

Date of filling the Proforma: _____Hospital HIMS No._____

Unique ID_____ Age _____ years

Gender

Male ☐

Female ☐

Marital Status

Married ☐

Unmarried ☐

Divorced/Separated ☐

Widowed ☐

Educational Attainment

Uneducated ☐

Primary School ☐

Secondary School ☐

College/Diploma ☐

University/Degree ☐

Postgraduate ☐

Occupation Group

Professional ☐

Managerial &Technical ☐

Skilled Non-Manual ☐

Skilled Manual ☐

Unskilled ☐

Not Applicable ☐

Occupational Status

Employed Full Time ☐

Employed Part Time ☐

Retired ☐

Unemployed ☐

Casual Worker ☐

Not working ☐

House Wife ☐

Other ☐

Monthly Income (In PKR)

Less than 5000 ☐

5000-10,000 ☐

10,000-20,000 ☐

20,000-50,000 ☐

more than 50,000 ☐

Ethnic Group

Muslim ☐

Non-Muslim ☐

Age at the onset of illness: _____ years

Duration of illness:

Less than one year ☐

One to 5 years ☐

More than 5 years ☐

Duration of treatment taken:

Less than one year ☐

One to 5 years ☐

More than 5 years ☐

Type of Oral SSRI treatment: (to be filled by the researcher)

Escitalopram ☐ Sertraline ☐

Fluoxetine ☐ Paroxetine ☐

Citalopram ☐ Fluvoxamine ☐

GROUPS:

A ☐

B ☐

SCORES OF HDRS:

At baseline: _____

After 3 and 6 weeks: _____

TREATMENT EFFECTIVE:

Yes ☐ No ☐

HDRS-17 (Hamilton Depression Rating Scale) – Template

Patient Unique ID: _____HIMS No.: _____

Date: _____ Clinician: _____

LEVEL OF ASSESSMENT

BASELINE ☐ At 3 weeks ☐ at 6 weeks ☐

HDRS-17 Scoring Sheet Template

Instructions: for each item select the one "cue" which best characterizes the patient.

DOMAINS	**SCORE (0—4)**
Depressed mood	0. Absent. 1.These feeling states indicated only on questioning. 2. These feeling states spontaneously reported verbally. 3. Communicates feeling states non-verbally, i.e. through facial expression, posture, voice and tendency to weep. 4. Patient reports virtually only these feeling states in his/her spontaneous verbal and non-verbal communication.
Feelings of guilt	0. Absent. 1. Self-reproach, feels he/she has let people down. 2. Ideas of guilt or rumination over past errors or sinful deeds. 3. Present illness is a punishment. Delusions of guilt. 4. Hears accusatory or denunciatory voices and/or experiences threatening visual hallucinations.
SUICIDE	0.Absent. 1.Feels life is not worth living. 2.Wishes he/she were dead or any thoughts of possible death to self.

	3. Ideas or gestures of suicide. 4. Attempts at suicide (any serious attempt rate 4).
4 Insomnia: early in the night	0. No difficulty falling asleep. 1. Complains of occasional difficulty falling asleep, i.e. more than half an hour. 2. Complains of nightly difficulty falling asleep.
5 Insomnia: middle of the night	0. No difficulty. 1.Patient complains of being restless and disturbed during the night. 2.Waking during the night – any getting out of bed rates 2 (except for purposes of voiding)
6. Insomnia: Early hours of the morning	0. no difficulty. 1. waking in early hours of the morning but goes back to sleep. 2. unable to fall asleep again if he/she gets out of bed.
7. Work and activities	0. No difficulty. 1. Thoughts and feelings of incapacity, fatigue or weakness related to activities, work or hobbies. 2. Loss of interest in activity, hobbies or work – either directly reported by the patient or indirect in listlessness, indecision and vacillation (feels he/she has to push self to work or activities). 3. Decrease in actual time spent in activities or decrease in productivity. Rate 3 if the patient does not spend at least three hours a day in activities (job or hobbies) excluding routine chores. 4. Stopped working because of present illness. Rate 4 if patient engages in no activities except routine chores, or if patient fails to perform routine chores unassisted.
8. Retardation	0.Normal speech and thought. 1. Slight retardation during the interview.

	2. Obvious retardation during the interview. 3.Interview difficult. 4.Complete stupor.
9. Agitation	0. None. 1.Fidgetiness 2. Playing with hands, hair, etc. 3.Moving about, can't sit still. 4.Hand wringing, nail biting, hair-pulling, biting of lips.
10. Anxiety Psychic	0. No difficulty. 1.Subjective tension and irritability. 2. Worrying about minor matters. 3. Apprehensive attitude apparent in face or speech. 4. Fears expressed without questioning.
11. Anxiety Somatic (physiological concomitants of anxiety) such as: gastro-intestinal – dry mouth, wind, indigestion, diarrhea, cramps, belching. cardio-vascular – palpitations, headaches Respiratory – hyperventilation, sighing.	0.Absent. 1. Mild. 2. Moderate. 3. Severe. 4.Incapacitating

urinary frequency sweating	
12. Somatic symptoms _ Gastro intestinal	0. None. 1. Loss of appetite but eating without staff encouragement. Heavy feelings in abdomen. 2. Difficulty eating without staff urging. Requests or requires laxatives or medication for bowels or medication for gastro-intestinal symptoms.
13. General somatic symptoms	0.None. 1.Heaviness in limbs, back or head. Backaches, headaches, muscle aches. Loss of energy and fatigability. 2. Any clear-cut symptom rates 2.
14. Genital symptoms (symptoms such as loss of libido, menstrual disturbance)	0. Absent. 1.Mild. 2.Severe.
15. Hypochondriasis	0.Not present. 1. Self-absorption (bodily). 2.Preoccupation with health. 3.Frequent complaints, requests for help, etc. 4.Hypochondriacal delusions.
16. Loss of weight [according to weekly measure]	0.Less than 1 lb. weight loss in week. 1.Greater than 1 lb. weight loss with in week. 2.Greater than 2 lb. weight loss in week. 3.Not assessed
17.Insight	0.Acknowledges being depressed and ill.

	1.Acknowledges illness but attributes cause to bad food, climate, overwork, virus, need for rest, etc. 2. Denies being ill at all.

Total Score: _____

Severity Interpretation (General Guideline):

0–7: Normal 8–16: Mild Depression

17--23: Moderate Depression 24 or more: Severe Depression

SCHEDULE OF REPORTING OF PARTICIPANTS DURING STUDY PERIOD

Unique ID _____ HIMS number _____

Group allocated	Schedule of follow up date for provision of psych biotic capsule / placebo capsule.	No of psychobiotic/ placebo capsules given.	Any untoward side effect/s reported by participant.

Side effects Reporting form:

Week	Side effects	Appetite changes	Sleep changes	Physical symptoms [fatigue, lethargy, headache	Allergic reactions	Severity [mild, moderate or severe]	Actions taken
	GI symptoms [Bloating, gas, nausea, diarrhea, constipation]						
1							
2							
3							
4							

Reasons for Drop out from study: [Tick relevant if applicable]

- ☐ Miss the follow up visit once.
- ☐ Doesn't respond to reminder calls / messages
- ☐ Develop untoward side effects that are source of distress.
- ☐ Requirement to increase or decrease the dose of an SSRI, or the need to add an adjunct antipsychotic or mood stabilizer