



Probiotic Supplements for Depression in Parkinson's Disease (Pro-Park): A Randomized, Triple-blind, Placebo-controlled, Phase IIb Trial Protocol

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Abstract

Introduction: Parkinson's disease (PD) is the second most prevalent degenerative neurological disorder globally. Comorbid major depressive disorder (MDD) is a common occurrence which adds considerably to disease burden. This protocol presents a study designed to investigate the effect of add-on probiotic supplementation on MDD in patients with PD.

Methods: We designed a phase IIb, randomized, triple-blind, placebo-controlled study to evaluate the efficacy and safety of probiotics as an adjuvant treatment to selective serotonin reuptake inhibitors (SSRI) for patients with mild to moderate PD and MDD. Participants will be randomized to probiotics (n=62) or placebo (n=62) arms using a permuted block randomization approach. Co-primary outcomes include changes in Montgomery-Åsberg Depression Rating Scale (MADRS) scores and SSRI equivalent doses, which will be compared between groups using a bivariate joint model. Secondary outcomes will include changes in both Beck Depression Inventory-II (BDI-II) score and levodopa dose, which will be analyzed using t-tests or Mann-Whitney tests as appropriate. Concurrent validity between MADRS and BDI-II will be assessed using Pearson's or Spearman's correlation tests. Safety will be evaluated by comparing discontinuation rates and adverse events between groups using chi-square. Data will be analyzed using intention-to-treat and per-protocol analyses, and missing data will be addressed using multiple imputation methods.

Discussion: Probiotics represent a potential new approach to managing depression in patients with PD by targeting the gut-brain axis. The results will offer crucial information about the safety and efficacy of a low-cost and readily available supplement that may alleviate depression in this vulnerable population.

Introduction

Symptoms of Parkinson's Disease (PD) are progressive and include both motor and non-motor symptoms. Around 38% of patients with PD experience

probiotics, SSRI, supplementation

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major depressive disorder (MDD) (Cong et al., 2022), which has a significant negative impact on subjective perception of disability, daily functioning, and quality of life (Assogna et al., 2020). MDD increases health-care consumption; amplifying costs and adding to the burden of disease experienced at both the individual and societal levels (World Health Organization, 2017).

The pathophysiology of depression in patients with PD differs from that of the general population (Ketharanathan et al., 2016). In these patients, the blood-brain barrier may be disrupted as a result of gut-derived inflammatory products, allowing dopaminergic loss to occur in the substantia nigra, leading to classic PD motor symptoms (Banks & Erickson, 2010). Serotonergic depletion in the raphe nuclei and noradrenergic loss in the locus coeruleus lead to behavioral symptoms and support the association of PD with MDD (Grosch et al., 2016). Although there are no standard guidelines for the treatment of depression in patients with PD, some studies suggest using SSRIs for treating MDD in this population (Pontone & Mills, 2021). Probiotic supplementation has demonstrated neuroprotective effects due to inhibition of pathogen colonization, modulation of the microbiome, immunomodulation, and improved host epithelial barrier function, leading to decreased accumulation of alpha-synuclein in both the enteric and central nervous systems (Tan et al., 2021). While the association between the use of probiotics and improved depression symptoms has been well established (El Dib et al., 2021), to the best of our knowledge, no study has been conducted to investigate the effect of probiotics on MDD in patients with PD.

This protocol was designed to investigate the efficacy of a commercially available blend of probiotics, Cerebiome®, as an add-on therapy to selective serotonin reuptake inhibitors (SSRI) compared to placebo plus SSRI in patients with mild-to-moderate PD and MDD. This particular commercial blend was selected because the dose and constituents are standardized and it has demonstrated efficacy for the treatment of MDD (Wallace & Milev, 2021). The objective of the proposed study is to determine if probiotics are clinically effective in reducing symptoms of depression in patients with PD and comorbid MDD after 3 months.

Materials and Methods

Trial Design

We report the design of a single center, phase IIb, randomized, triple-blind, placebo-controlled, parallel-group, superiority trial, with a two-week run-in phase.

Eligibility Criteria

Adults with clinically diagnosed MDD and mild-to-moderate PD (Hoehn and Yahr stages I-III) (Clarke et al., 2016) and stable treatment with SSRI will be included. Exclusion criteria will be cognitive impairment, neurological disease other than PD, primary gastrointestinal diseases, and recent (within the last 12 weeks) use of probiotics (full inclusion and exclusion criteria in Table S1).

Recruitment Strategy

Participants will be recruited via investigator-based subject recruitment from inpatient and outpatient neurology and psychiatry departments at a single university hospital.

Randomization Sequence Generation

A central randomization approach will be used. Participants will undergo permuted block randomization, with allocation to either of the two treatment arms in a 1:1 ratio. The study will use an electronic Case Report Form (e-CRF) system (EOL Random©, Medsharing, Fontenay-sous-Bois, France) to electronically generate an unpredictable allocation sequence based on the block randomization approach and the predetermined sample size. For each randomized number generated, a corresponding code will be generated by the e-CRF which will allocate the participant to the intervention or the control groups.

Allocation Concealment

All eligible participants will be randomized. A random allocation sequence with a permuted block approach (four or six subjects per block) will be used to ensure participants' group allocation cannot be predicted. An independent researcher will generate the allocation sequence and randomization table. The e-CRF system will be installed in a password-protected computer connected to the hospital intranet but not connected to the global internet. A statistician without access to data analyses will manage the electronic allocation sequence which will be maintained within the e-CRF system. Block sizes will not be disclosed to participants or researchers to ensure allocation concealment.

Blinding

The clinical trial will be triple-blind. Participants, investigators involved in the treatment or clinical evaluation of participants, and the main statistician

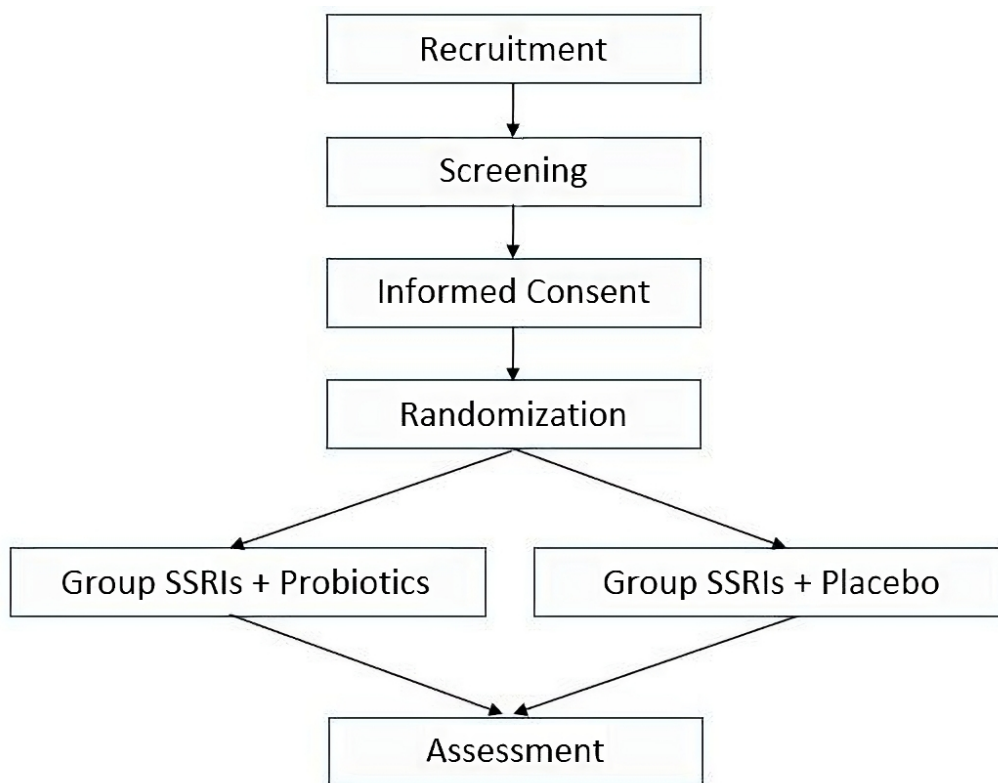


Figure 1: Study flowchart.

will not be informed about treatment allocation until the end of the study. Probiotic and placebo capsules will be identical in appearance and will be packed in identical primary and secondary packaging. Each participant will receive the capsules in a blister pack labeled with only the participant's identifying number, the trial name, and the expiration date. The randomization sequence will only be disclosed to the pharmacist responsible for dispensing the placebo or probiotic treatments. If a serious adverse event occurs (see discontinuation section), blinding can be broken by order of the treating physician or data monitoring committee, if deemed necessary, through the e-CRF.

Adherence

A study information package will be created with key information about the protocol, including clear instructions about participation in the study. It will be given to participants and/or their caretakers during visit 1. In addition, biweekly phone calls will be made by a study nurse at a predetermined time to assess participants' protocol adherence and identify any barriers to following the study directions. To verify adherence, during the biweekly phone calls, participants will report the number of remaining capsules and the study nurse will then inform the participant how many capsules they should have

left. At each site visit, each participant will return their blister pack. The study pharmacist will count the remaining capsules to determine whether the participant has adhered to the dosing schedule. Participants will also have access to a hotline number, which will be operated during business hours, where they can ask questions and raise concerns.

Timeline

The study has a two-week run-in period to assess compliance before randomization. The duration of the study will be 3 months from randomization to cut-off. We selected a 3-month follow-up based on the observed efficacy of probiotics in managing depression across various populations within the same timeframe (Majeed et al., 2018). The study flowchart is shown in Figure 1, and the site visit schedule is shown in Table S2.

Assessment Visits

All assessment visits will be conducted either on-site or remotely via a Health Insurance Portability and Accountability Act (HIPAA)-compliant telehealth platform. Site visits which do not require neurological examination will be remote. Participants without access to a computer will be supplied with a locked tablet with internet connection.

Data Collection

The following demographic data will be collected via participant interview and chart review during site visit 2: participant age (years), sex (male or female), ethnicity (Caucasian, Black, Asian, other), dependency on caretaker (yes or no), height (centimeters), weight (kilograms), smoking status (never, former, active), alcohol use (yes or no), comorbidities (yes or no, type), current use of antidepressant medication (total number of medications, type, and schedule), current stage of PD (Hoehn and Yahr scale [Clarke et al., 2016]), physical activity (Modified Parkinson Activity [Taniguchi et al., 2021]), time since PD diagnosis (months), and current anti-Parkinson medications (name and dose). At site visits 4 and 5, MADRS score (Ketharanathan et al., 2016), BDI-II score (Steer et al., 1997), SSRI dose change (yes or no), levodopa dose, adverse events, and/or reason for withdrawal will be collected.

Treatment Arms

Participants will be assigned to one of two treatment arms. The intervention group will receive probiotics plus SSRI of physician's choice. The control group will receive placebo plus SSRI of physician's choice. The intervention group will receive Cerebiome® capsules (Lactobacillus helveticus Rosell®-52 and Bifidobacterium longum Rosell®-175, 3 billion CFU each per capsule) (Wallace & Milev, 2021). The control group will receive sham capsules containing only excipients (xylitol, maltodextrin, plum flavor, and malic acid) (Romijn et al., 2017), which will be sensorially identical to the intervention. Lallemand Health Solutions Inc. (Mirabel, Canada) will supply both the study product in its commercially available form and the placebo, labeled in accordance with the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines.

Administration

Participants in both groups will ingest one capsule orally daily one hour before, or two hours after eating. The capsule will be taken 2 hours after scheduled antiparkinson medications to avoid interactions. The first capsule will be taken within 24 hours of site visit 3 and continued for three months.

Dose Modifications

Dosage modification of the intervention or placebo

will not occur at any time during the trial.

Discontinuation

Participants will be withdrawn from the trial at the participant's or treating physician's request or if any of the following events occur: (a) death; (b) life-threatening infection (e.g., sepsis or septic shock); (c) severe dehydration or hypovolemic shock secondary to acute or persistent diarrhea (Riddle et al., 2016); (d) acute abdominal pain of nontraumatic origin for a minimum duration of 5 days; (e) urgent medical condition requiring treatment within 24 hours (Gans et al., 2015); (f) antibiotic use; (g) change in class of primary antidepressant treatment; or (h) other serious medical events determined by the investigator or treating physician to warrant withdrawal from the study. Adverse events may result in the temporary or permanent withdrawal of a participant from the trial at the discretion of the primary physician or main investigators. All grade 3-5 adverse events (Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0, 2017) will be reported to the data monitoring committee within a period of 48 hours. The entire trial will be discontinued if over 50% of participants develop grade 3-5 adverse events because it will be determined that the risks of participation outweigh the potential benefits.

Primary Outcomes

Coprimary outcomes, MADRS and changes in SSRI equivalent doses, will be evaluated at baseline and 3 months. The MADRS is composed of 10 items, which are rated from 0-6, with total scores ranging from 0 to 60 points (Ketharanathan et al., 2016). Changes in SSRI equivalent doses will be collected as a binary variable: yes, for any dose increasing or decreasing, and no for no changes. Dose equivalency among SSRIs will be defined according to the dose conversion algorithm published by Furukawa et al. (2019). The mean MADRS score changes and changes in SSRI equivalent doses will be compared between groups. As the SSRI dose may be adjusted by the physician during the study period, assessing only the MADRS score may not reflect the full effect of the intervention, therefore a co-primary outcome approach will be used.

Secondary Outcomes

- Depression assessment: Depression will also be evaluated using the BDI-II at baseline and 3 months. The BDI-II is a 21-item self-reported scale, with a

maximum score of 63 points which has been validated for individuals with Parkinson's disease (Steer et al., 1997). The BDI-II mean score change will be compared between groups. The mean MADRS score change alone will be compared between groups at 3 months. To assess concurrent validity, the BDI-II will also be compared to the MADRS mean score change.

- **Disease progression:** Levodopa dose increases as PD progresses and will therefore be used as a surrogate for changes in disease severity. Each participant's levodopa dose will be recorded at baseline and 3 months. The difference between doses at each time-point will be assessed by researchers during data analysis. Change in levodopa dose will be reported as the mean variation in milligrams per day (e.g., $\Delta\text{mg}/\text{day}$ 3 months = mg/day at 3 months - mg/day at baseline).

- **Tolerability:** Whether a participant remains in the study or discontinues will be recorded as frequency (%) during each site visit and compared between groups. The reasons for dropouts will also be determined and reported as frequency (%) and will be compared between groups.

- **Adverse Events:** Any adverse events experienced by the participants will be documented by them in a study diary each night. During study visits 4 and 5, each participant will be asked to show their study diary. They will also be questioned about adverse events experienced using a standardized list of adverse events of special interest, including nausea and vomiting, flatulence, abdominal cramps, hyporexia, dysgeusia (Lerner et al., 2019), diarrhea, and brain fog (Lerner et al., 2019). Adverse events will be classified as Grade 1 (mild), 2 (moderate), 3 (severe), 4 (life-threatening), or 5 (lethal) according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5 or the most recent publication (Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0, 2017). The type, grade, and frequency (%) of adverse events will be compared between groups.

A full description of the outcomes can be found in Appendix 1.

Data Management

Data will be collected and entered into the electronic system by the data coordinating nurse/research nurse or the designated investigator at the study site. Participants' non-identifiable information will be provided to the investigators, research staff, and statistician. Original study documents will be filed securely.

Data Monitoring

A Data Monitoring Committee will independently assess the safety, validity, and integrity of the study data.

Sample Size Calculation

Sample size was estimated using an effect size ≥ 4.5 points difference in the MADRS between placebo and active treatments, a power of 80% with a 5% (0.05) two-sided alpha level, and the variance derived from a pooled standard deviation of 6.89, based on a previous study by Majeed et al. (2018). We determined that 46 individuals per arm were required for the trial. The predicted dropout rate was set at 25%. Therefore, the final target sample size was fixed at 62 individuals per arm (124 individuals in total).

Statistical Analysis

A p-value less than 0.05 will be considered significant in all tests and a 95% confidence interval (CI) will be adopted for measuring the range of treatment effect. Absolute and relative frequencies will be used to describe categorical variables. The Shapiro-Wilk test will be used to assess normality, and data with normal distribution will be presented by mean and standard deviation. Data with non-normal distribution will be presented as median and interquartile range.

A bivariate joint model will be used to assess the co-primary outcomes (MADRS score and SSRI equivalent dose change) following the process outlined by Teixeira-Pinto et al. (2009) and Teixeira-Pinto & Mauri (2011). Linear regression will be used to assess changes in MADRS score and logistic regression will be used for changes in SSRI equivalent dose. A latent variable will be created and used to connect both models in a single statistical analysis and modeled using a multivariate normal distribution.

For the secondary outcomes, variation in the BDI-II scale during the follow-up period (3-month follow-up minus pre-test) will be compared between groups using unpaired t-test or Mann-Whitney test. The same approach will be used to assess differences in MADRS during the follow-up period. The concurrent validity with MADRS and BDI-II scores will be assessed using Pearson's or Spearman's correlation tests depending on the normality of distribution. To assess changes in levodopa dose, unpaired t-test or Mann-Whitney test will be selected as appropriate. Chi-square test will be used for between-group comparisons of discontinuation as well as adverse events.

Missing Data

All data will be analyzed primarily using an intention-to-treat analysis strategy. A per-protocol analysis approach will be conducted to assess confidence in the results. The strategies which will be used for managing missing data using multiple imputation methods and sensitivity analyses are represented in the algorithm shown in Figure S1.

This study protocol will be reviewed and approved by the local Institutional Review Board (IRB). All procedures performed in this study involving human participants will be conducted in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Before participating in the study, all participants will be provided with a detailed explanation of the study objectives, procedures, potential risks, and benefits. Written informed consent will be obtained from all individual participants included in the study. Participants will be assured that their participation is voluntary, and they may withdraw from the study at any time without any consequences.

Discussion

MDD is a common comorbidity of PD requiring effective and accessible treatment. This protocol provides a roadmap to assess the efficacy and safety of add-on probiotics for treating MDD in patients with PD.

A major strength of the protocol is the use of co-primary outcomes with joint modeling. The first co-primary outcome is the MADRS, which is widely used in clinical research to assess depression owing to its high specificity and sensitivity (0.995 AUC in PD). The MADRS was selected for this study because it relies on observer ratings and assesses fewer somatic symptoms. This helps avoid overestimating depression in patients with PD (Ketharanathan et al., 2016).

The other co-primary outcome is change in SSRI equivalent dose. This measure accounts for alterations in depression severity which are tempered by SSRI changes. By employing a dual primary outcome framework, we potentially increase the likelihood of detecting efficiency and may also reduce the severity of multiple testing corrections required by managing correlation between endpoints.

Our secondary outcomes serve two purposes: validating the results of the primary outcome and generating exploratory data for future clinical investigation. Clinician-rated and self-reported scales differ in how they detect changes in symptoms (Demyttenaere & Jaspers, 2020). The BDI-II, a validated and commonly used self-reported tool in PD (Stohlman et al., 2021),

was selected as a secondary outcome to validate the results of the MADRS score. Changes in levodopa dose serves as a surrogate outcome to assess the progression of PD symptoms. The tolerability and safety of the intervention will also be assessed as secondary outcomes to provide important safety assessments.

This protocol has limitations. The primary weakness of the statistical plan is the lack of consensus on sample size determination considering the presence of co-primary outcomes and the need for joint modeling to assess the primary endpoint. In addition, the sample size calculation was not based on a power analysis for running a joint model with a latent variable.

The results of this study will contribute important data to inform the treatment of patients with PD and comorbid MDD. Positive findings may provide evidence that probiotics are a safe, effective, and affordable approach to reduce depression in patients with PD. On the other hand, negative results would still provide useful efficacy and/or safety data and may prompt future research and decrease the knowledge gap in this area.

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Conflicts of Interest

The authors declare no conflict of interest.

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