Letter to the Editor

Reply to: Toward Enhanced Methodological Rigor: Addressing Limitations in the Comparative Analysis of Probiotics and Antidepressants for Major Depressive Disorder Management

Dear Editor,

In our recent study,[1] we pooled data from 42 double-blind, randomized clinical trials (RCTs) to compare the efficacy and acceptability of probiotics and antidepressants in treating major depressive disorder (MDD) in adults. Given the absence of head-to-head RCTs and considering the potential ethical issues, we undertook a network meta-analysis to evaluate the non-inferiority of the 2 interventions by indirect comparisons. In response, de Souza Junior et al[2] pointed out several potential limitations in our methodology. We appreciate their insightful comments on clinical applications of our findings.

Homogeneity within a meta-analysis is crucial for drawing reliable conclusions, particularly concerning the homogeneity of patient characteristics (eg, types of depression, severity of MDD, diagnostic criteria, demographics), interventions (eg, types of antidepressants, dosage, concurrent medication use), outcomes (assessment tools), and study design (eg, randomization, concealment, blindness, sample size). However, the heterogenicity is inevitable because clinical and methodological diversity always occur in a meta-analysis.[3] Accordingly, we conducted a series of subgroup analyses, meta-regressions, and sensitivity analyses to identify and address sources of heterogenicity.

HOMOGENEITY OF PATIENTS

Concurrent medication uses

de Souza Junior et al[2] argue that concurrent medication use would complicate data interpretation. However, participants in both the antidepressants and probiotics arms were not receiving other concurrent treatments, such as psychotherapies. Additionally, most trials reported restrictions on concurrent medication use in their eligibility criteria, including the prohibition of psychoactive medications or a mandatory washout period before the study, thus enhancing the reliability of our findings.

Inadequate characterization of patient clinical profiles and diagnostic criteria

We applied the data extraction for complex meta-analysis guide,[4] a referenced data-collection template for network meta-analysis during data extraction and adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses network meta-analysis checklist.[5] We also included participants' age in the meta-regression and pooled data that were published before 2015. Still, neither factor led to a different conclusion, demonstrating the robustness of our results.

HOMOGENEITY OF INTERVENTIONS

Concomitant antidepressant use

Some studies included in our analysis did not clearly report the details on concomitant use of antidepressants. Of note, only 1 trial investigated the efficacy of probiotics as a stand-alone treatment. To avoid the unpredictable consequences of inactive treatments, we included studies in which participants took other antidepressants. This lack of clarity complicates the interpretation of results. We support the call for more standardized approaches to data collection (eg, clear and detailed concomitant antidepressants use) in future research to ensure that study findings are reliable and clinically meaningful. Moreover, because there was the limited number of stand-alone probiotics trials, the subgroup analysis showed that probiotics as an adjunct therapy would be efficacious for treating MDD.

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Augmentation therapies

The selection of antidepressants for our analysis was guided by the most comprehensive network meta-analysis of the management strategies for MDD and the latest clinical practice guidelines from the US Department of Veterans Affairs and US Department of Defense.[6,7] First, differentiating treatment-resistant depression (TRD) and inadequate response to antidepressants is necessary. The most common TRD definition for major depressive disorder includes a minimum of 2 prior treatment failures and confirmation of prior adequate dose and duration.[8] In contrast, an inadequate response to antidepressants can be characterized as failing to achieve complete remission of symptoms despite 1 course of treatment being administered properly.[9] In our included RCTs discussing augmentation therapies, the participants did not meet the TRD diagnostic criteria. Although the inclusion of augmentation therapies may complicate the interpretation of the results, in order to compare the effectiveness of probiotics with currently available therapies among people with depression disorders as much as possible, we did not exclude these data. Our results showed that probiotics are more common as adjunctive therapies in treating MDD. In addition, pilot trials suggest probiotics may benefit TRD.[10,11] However, we did not include those trials, because of the ineligibility of study design and the participants with TRD. Moreover, the small sample sizes in these pilot studies underscore the need for further research involving larger populations and more rigorous experimental designs.

Doses of antidepressants

We acknowledge concerns regarding different doses of antidepressants used in some studies. To clarify, Harvey et al[12] used duloxetine as a positive control, with a regimen of 60 mg orally for up to 8 weeks, followed by a taper-down period of 30 mg daily for 1 week. The varied doses, indeed, could have contributed to attenuated treatment responses. Our analysis aimed to reflect real-world clinical scenarios where varying doses are common. Unfortunately, the limited number of RCTs constrained our ability to perform a subgroup analysis using dosage as the factor or to conduct dose-responses meta-analysis.

ISSUES OF STUDY DESIGN

Rigorous study design and methodology assessment

We strived to include studies with robust methodologies but acknowledge that biases cannot be completely eradicated. Therefore, we recommend that future studies use rigorous randomization techniques and transparently report any potential sources of bias. The low confidence ratings assigned to some comparisons underscore the challenges inherent in synthesizing heterogeneous data, necessitating cautious interpretation of results and highlighting the importance of conducting high-quality, homogeneous research.

Small sample size in probiotics trials

Our study underscored that microbiota-targeted therapies for MDD are an emerging field, characterized by trials with small sample sizes. These trials often have limited evaluations on dosage, frequency, and individual probiotic strains. However, using Hedge's g rather than Cohen's d to calculate the standard mean difference allowed us to correct for potential biases due to small sample sizes. To advance the understanding and effectiveness of these interventions, research is needed that involves large-scale studies that not only expand sample sizes but also enhance the dosage and strain-specific evaluations.

CONCLUSION

In conclusion, we appreciate the constructive feedback from de Souza Junior et al.[2] We agree that some clinical and methodological characteristics, such as the dose of antidepressant use between studies, could be different, as could the patient clinical profiles and diagnostic criteria. However, differences among these characteristics are inevitable when we need to conduct a meta-analysis of complex diseases like MDDs. Achieving perfect homogeneity and transitivity in characteristics of patients and interventions in a network meta-analysis is not always feasible. Nevertheless, the growing interest in probiotics, along with their potential efficacy with reduced stigma in managing MDD, underscores the importance of further exploration into this area. We hope this discussion will incite researchers to conduct well-designed, large-scale RCTs to investigate the therapeutic benefits of microbiota-targeted therapies for MDD.

Author Contributions

H.M.T. and S.Z. conceived and designed this work. S.Z. performed data collection and analysis and drafted the manuscript. J.T., S.L., and H.M.T. reviewed the manuscript and provided comments. All authors read and approved the final version of the submitted manuscript.

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Conflicts of Interest

H.M.T. is named as an inventor on the patent applications held by the Chinese University of Hong Kong and Microbiota I-Center that cover the therapeutic and diagnostic use of microbiome. The other authors have nothing to declare.

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