

Treatment of Anxiety with Fecal Microbiota Transplantation: A Critical Review

Ana Pamela Gómez García¹, María Magdalena Aguirre García^{1*} and Álvaro Zamudio Tiburcio^{2*}

¹Unidad de Investigación UNAM-INC, División de Investigación, Facultad de Medicina, UNAM, Instituto Nacional de Cardiología Ignacio Chávez, Ciudad de México, México

²Department of Gastroenterology, Intestinal Microbiota Transplantation Unit, (Medical Specialties Naples), Mexico City, Mexico

***Corresponding Author:** María Magdalena Aguirre García, Unidad de Investigación UNAM-INC, División de Investigación, Facultad de Medicina, UNAM, Instituto Nacional de Cardiología Ignacio Chávez, Ciudad de México, México and Álvaro Zamudio Tiburcio, Department of Gastroenterology, Intestinal Microbiota Transplantation Unit, (Medical Specialties Naples), Mexico City, Mexico.

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Abstract

Introduction: The significant relation between the intestinal microbiota and the brain is based on bidirectional communication through the microbiota-gut-brain axis. Anxiety can stem from an imbalance in this axis, together with other factors. Since about 15% of the world population suffers anxiety, it is necessary to seek effective solutions to what is now a growing public health issue. Fortunately, promising treatments for anxiety disorders are being developed. One prominent therapy is the restoration of the intestinal microbiota by intestinal microbiota transplantation (IMT).

Objective: To examine the advantages and disadvantages of treating anxiety with IMT by analyzing related articles.

Methods: An extensive search of the literature was conducted in the PubMed and Cochrane Library databases to find relevant reports published from 2015 - 2021. The following themes were sought in the abstract or title: IMT, anxiety, and various alternative treatments for modifying the intestinal microbiota.

Results: Of the 58 articles generated by the search, 7 were found to be suitable for the present review, considering the inclusion criteria. Four of the latter studies were quantitative, of which one was a clinical trial and the other three consisted of experiments on mice. All these quantitative studies considered fecal microbiota transplantation (FMT) to be advantageous for the treatment of anxiety.

Conclusion: FMT is useful for the clinical management of anxiety. The highly effective outcome far exceeds the importance of the few possible complications. Indeed, the majority of the complications are reversible. Avoiding the administration of antibiotics is recommended for this procedure.

Keywords: Anxiety; Intestinal Microbiota; Fecal Microbiota Transplantation; Microbiota-Gut-Brain Axis; Meta-Analysis

Introduction

Intestinal microbiota transplantation (IMT) is a practice dating back thousands of years, having been carried out in China over 2,000 years ago and in India ~3,000 years ago. In regard to modern medicine, it was first employed in 1958 through a retention enema to treat a *Clostridium difficile* infection in Denver, Colorado, USA. Subsequently, it has been successfully used to treat various disorders including anxiety.

A significant relation exists between the intestinal microbiota and the brain, based on the bidirectional communication through the microbiota-gut-brain axis [1]. Anxiety can stem from an imbalance in this axis due to diet and other factors [2]. Around 15% of the population suffers from anxiety, which is now a growing public health problem [3]. This disorder is associated with irritable bowel syndrome, inflammatory bowel disease, and other pathologies [4,5]. Among the novel methods developed for the treatment of anxiety disorders is the modulation of the intestinal microbiota by intestinal microbiota transplantation (IMT) [6].

The present analysis was in great part inspired by numerous articles indicating that the intestinal microbiota can play an important physiological role in disease, including anxiety [7,8]. There is evidence of the involvement of the brain in the host-microorganism interaction [9-13], which is known to take place through various pathways such as immune mediators, hormones, and neurons [14,15]. For example, inflammation of the digestive apparatus alters the biochemistry of the central nervous system (CNS) in a manner similar to that found with anxiety [16-19].

Methods

Literature search

To download articles related to IMT as a therapy for anxiety, an extensive search of the literature was carried out based on the following terms: IMT, fecal microbiota transplantation (FMT), fecal bacteriotherapy, fecal infusion, installation of processed feces, infusion of fecal suspension, IMT and anxiety, and IMT and meta-analysis. Articles were considered if they mentioned anxiety and some IMT treatment in the title and/or abstract and were published from 2015 - 2021. Excluded from the current analysis were studies having less than ten subjects, less than four parameters for the diagnosis of anxiety, and/or inadequate protocols. Also excluded were reviews without a systematic methodology.

The literature search was conducted independently by two of the authors according to a previously established strategy. When differences existed between the two searches, the corresponding articles were reviewed by both authors participating in this phase and an agreement was made as to relevance.

Extraction of data

For the extraction and verification of data, the parameters considered were the study design, number of subjects, methodology, medical intervention, and results. All authors independently evaluated each report for the risk of bias based on the recommendations of the Jadad scale for standards of quality in clinical trials.

Results

Literature search

The search in the PubMed and Cochrane Library databases detected 48 and 9 articles, respectively, for a total of 57. Three duplications reduced the number to 54. After reading the title and abstract of each article, 34 were excluded as irrelevant to the subject at hand. Finally, a reading of the complete text of the 20 remaining articles led to the elimination of 13 more (in accordance with the exclusion criteria), leaving only 7 for the current review (Figure 1).

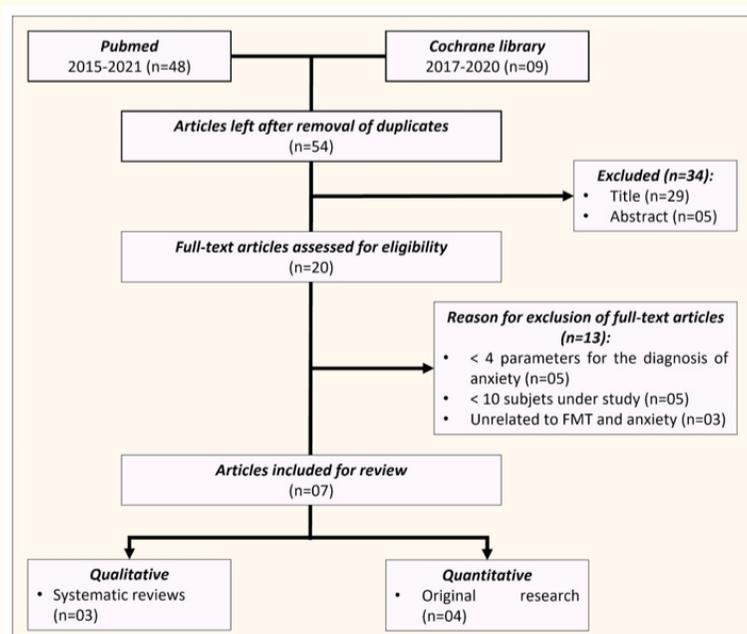


Figure 1: Flowchart of the study. Of the 57 articles downloaded during the search of two databases, 7 studies were selected for the present critical review. FMT: Fecal Microbiota Transplantation.

Basic characteristics of the reports included

Of the four quantitative studies included, only one (Kilinçarslan S and Evrensel A. 2020) was carried out on patients. All ten patients, diagnosed with irritable bowel syndrome, were given FMT to treat their condition. Subsequently, an examination was made of changes in the severity of patient depression, anxiety, and obsession. The other three quantitative studies were conducted on mice (203 animals), applying experimental murine models of FMT.

A score of 1 (“low”) on the Jadad scale for the clinical trial reveals its poor quality. A detailed description of the methods of random selection were not provided. Moreover, the study lacked a blind outcome assessment, and abandoned some of the subjects. On the other hand, the studies with murine models were longitudinal and based on random distribution into the experimental and control groups. However, the Jadad scale is limited to randomized, controlled clinical trials.

Therapeutic effects

According to Shan., *et al.* [19], the animal feed (with lactate) and the IMT procedure caused psychomotor discomfort as well as problems of learning and memory in the animals. They concluded that the resulting chronic stress could have altered the composition of the intestinal microbiota, and that the corresponding microbial products may have transmitted signals to the CNS capable of inducing anxiety in the animals.

After performing FMT, Marcondes., *et al.* [22] confirmed the bidirectional nature of the signaling involved in the microbiota-gut-brain axis, which was transmitted through the vagus nerve. Li., *et al.* [23] explored whether or not the gastrointestinal microbiota is a decisive factor in anxiety- and depression-like behavior, as well as its impact on the neurochemistry of the brain. They observed anxiety- and depression-like behavior in mice submitted to IMT. Zhao., *et al.* [24] found a sharp and significant increase in *Firmicutes* and decrease in *Bacteroidetes* in the intestinal microbiota of the mice that underwent transplantation of the intestinal microbiota from alcoholic patients (compared to the control animals without IMT). Additionally, the same experimental group showed anxiety, depression, and a strong tendency to drink alcohol. According to the authors, the transplant induced a state of dependency on alcohol, possibly through a diminished expression of BDNF, α 1GABAAR, and mGLUR1.

Kilinçarslan and Evrensel [26] observed a decrease in anxiety and other mental disorders after IMT was given to patients, owing itself to the direct neuropsychiatric effects of the procedure and to an improvement in gastrointestinal symptoms. These effects were independent of other circumstances. Meyyappan., *et al.* [27] emphasize the usefulness of FMT for correcting or reducing the impact of various neuropsychiatric disorders (e.g. anxiety). Generoso., *et al.* [28] showed that the interaction between the intestinal microbiota and the corresponding epithelium can cause physiological changes in the brain and alterations in mood and behavior.

As Wagner-Skacel., *et al.* [25] pointed out, numerous sources have described the involvement of the intestinal microbiota in the regulation of metabolic, immune, and digestive functions as well as sleep and one’s mental state. Such regulation takes place through the microbiota-gut-brain axis. By reviewing five years of publications in PubMed (ending in 2020), this research group found two cross-sectional studies correlating diseased states to sleep disorders. The first was conducted on 154 bipolar patients and the second on patients with irritable bowel syndrome. Tian., *et al.* [20] examined 34 patients with functional constipation treated with endoscopic IMT. Before and after treatment, evaluations were made of intestinal motility as well as anxiety and depression with the Zung Self-Rating Depression scale. The clinical cure rate for the treatment was 73.5%, with 14.7% clinical remission and 11.8% clinical inefficiency.

Comments

In numerous publications, the impact of FMT on diverse disorders is mentioned. Among these, the studies exploring the effect of FMT on anxiety [29-31] stand out due to the highly effective outcome that by far exceeds in importance the few possible complications. It is

necessary to choose properly from the available procedures, which include endoscopy, retention enema, and capsules [32,33], carried out with or without antibiotics [34,35]. Hence, FMT is advantageous for treating anxiety both experimentally (in mice) and clinically. It is crucial to have an excellent donor, perfectly studied and controlled through trimestral lab tests. Moreover, the patient must be given strict follow-up. Although supplementary treatments can be provided, they tend to substantially increase the cost of therapy [36,37].

Conclusion

FMT is a useful procedure for the clinical management of anxiety. The majority of the most common complications that may arise during FMT do not negatively affect the procedure because of being reversible. It is beneficial for patients with anxiety that are under FMT treatment to receive probiotics, prebiotics, synbiotics, and other biotics, while the administration of antibiotics should be avoided.

One limitation of the present review is the inclusion of only one clinical trial. There is a need for more double-blind, randomized clinical trials with a good design in order to furnish a greater quantity of hard data capable of expanding the current knowledge of the effects of FMT in the clinical management of anxiety.

Conflicts of Interest

The authors declare that they do not have any affiliation with or participation in organizations having a financial interest in the conclusions or publication of the current research.

Ethical Approval

This report does not contain any study with human or animal subjects that was carried out by the authors.

Informed Consent

No informed written consent from patients was needed to develop this article.

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