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# 1 PSYCHIATRIC ILLNESSES AND GUT MICROBIOME

Fecal microbiota transplantation and gut microbiome effects on psychiatric illnesses

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### **Abstract**

Despite the medical advances that have been made in regards to mental health, psychiatric medications, and alternative therapies, many patients continue to suffer day in and day out, unable to live the type of life they desire. Many times, the medication route includes many episodes of trial and error, side effects, and no significant improvement in actual symptoms. Therapy, although effective, typically necessitates a supplemental medication for the best results. Fecal microbiota transplantation (FMT) is a method where feces from a healthy donor is transferred to an affected patient, typically via colonoscopy. Theoretically, this alters the gut microbiome in a positive way to alleviate symptoms. With the help of three studies, this theory was suggested to improve symptoms. These three studies utilized humans and mice, and each used a unique way to decipher the question if transferring healthy stool to a recipient will positively alter gut microbes and in turn lead to improved mental health symptoms. Although this procedure is considered experimental and more research must be done, FMT for mental health is a massive medical milestone that provides hope for the future.

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Improvement in psychiatric illnesses and gut microbiome post fecal microbiota transplantation

According to the Anxiety and Depression Association of America, nearly 40 million people in the United States experience an anxiety disorder in any given year (NIH, 2017).

Additionally, an estimated 17.3 million adults in the United States had at least one major depressive episode. This number represents 7.1% of all U.S. adults (NIH, 2019).

The human intestine harbors many microbes that carry out various roles in the body and have systemic influences outside of the gastrointestinal tract (Thomas, 2018). There are  $10^4$  gut microbes that are essential to human health and prevent diseases, aid in immunity, produce vitamins, maintain the epithelial barrier, and produce substrates for the enterocytes (Thomas, 2018). When this fragile balance of microbes is disturbed, whether it be due to antibiotics, restrictive diets, or vaccines, it can disrupt the composition and functions of the gut microbes, with these microscopic changes leading to various manifestations, including mental health (Appleton, 2000). This is where a fecal transplant can be performed. Fecal microbiota transplantation is used as a treatment for patients with chronic and refractory *Clostridium difficile* infection, a bacterium that can cause symptoms ranging from diarrhea to life threatening inflammation of the colon (Clapp, 2017). During a fecal transplant, a slightly processed form of feces from a healthy donor is transferred to an affected patient, typically via colonoscopy, capsule ingestion, flex sigmoidoscopy, or enema. This restores the stable community of essential gut microbes and allows them to flourish, returning the patient to a healthy state (Thomas, 2018).

Scientists have established that there is indeed a link between the gut microbiome and mental health, termed the gut-brain-axis (Carabotti et al., 2018). Through a systematic review of the available published research reports regarding FMT, the gut microbiome, and depression,

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study results will be summarized and synthesized to better understand the clinical implications of this recent advancement in medicine.

##### **Materials and Methods**

Three different studies were utilized and the findings were summarized to help aid in the research question. A broad search was conducted to ensure that these three studies were the best available at the time in terms of subjects used, year conducted, and resemblance to the research question in order to yield the best outcome. These three papers were thoroughly read and studied for credibility, feasibility, and value, and the combined findings were used to decipher the research question.

Google Scholar and the Dominican University of California library A-Z Database was utilized in the search. The filters were adjusted to include studies published in the last 30 years, and key terms such as “FMT”, “gut microbiome”, and “mental health” were searched to generate papers that were both recent and in line with the topic. Roughly 100 papers were sifted through until the 3 studies were selected.

The first study was, The effect of fecal microbiota transplantation on psychiatric symptoms among subjects with irritable bowel syndrome, functional diarrhea and functional constipation: An open-label observational study, from the *Journal of Affective Disorders*. In this small study subjects (n=17) with irritable bowel syndrome, functional diarrhea, or functional constipation underwent FMT for the purposes of treating gastrointestinal symptoms and observation of mental health effects. Baseline mental health was studied before and after FMT using the Hamilton Rating Scale for Depression (HAM-D), sleep subscale score, Hamilton Rating Scale for Anxiety (HAM-A), and Quick Inventory for Depressive Symptoms (QIDS) (Kurokawa et al., 2018).

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The second study was, Transferring the blues: Depression-associated gut microbiota induces neuro-behavioral changes in the rat, from the *Journal of Psychiatric Research*. In this small study, fecal samples were collected from subjects (n=34) with major depressive disorder (MDD) and additional subjects (n=33) without a mental health diagnosis. A FMT was transferred to a microbiota deficient rat model and studied (Kelly et al., 2016).

In the final study, Gut microbiome remodeling induces depressive-like behaviors through a pathway mediated by the host's metabolism from *Molecular Psychiatry*, microbial communities of subjects (n=55) with MDD and healthy controls (n=63) were obtained. A FMT was done from MDD subjects or healthy subjects to mice. Behavioral testing was then done to assess depression-like symptoms in the mice (Zheng et al., 2016).

### **Results**

The three studies demonstrated a significant link between FMT and improvement in gut microbiota and mental health. The first study published in the *Journal of Affective Disorders* suggested that depression and anxiety symptoms are improved by FMT regardless of gastrointestinal symptom change in subjects with IBS (irritable bowel syndrome), FDr (functional diarrhea) and FC (functional constipation). The link was thought to be due to the increase of microbiota diversity that helped improve the subjects' mood (Kurokawa et al., 2018).

The second study published in the *Journal of Psychiatric Research* suggested that the gut microbiota may play a causal role in the development of features of depression and may provide a tractable target in the treatment and prevention of this disorder (Kelly et al., 2016).

The third study published in *Molecular Psychiatry* showed that the composition of gut microbiota is significantly altered in MDD human subjects compared to healthy controls and that this composition is transmissible to mice. It showed that colonization of mice with 'depression

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microbiota' resulted in increased depression-like behaviors as compared with colonization with 'healthy microbiota' (Zheng et al., 2016).

Although this is minimal data and much more research must be performed, the available evidence suggests that there is indeed a link between the gut microbiome and mental health and that this gut flora can be transferred person to person. The combined results of these 3 studies points towards there being some sort of alteration that takes place in the recipients' gut following a FMT. The sample that is transferred can be selected from a "healthy" donor, and their flora can help aid in the improvement of the mental health disorder the subject is suffering from.

### **Discussion**

FMT for the sole purpose of evaluating mental health changes is still considered highly experimental. Scientists face many barriers and approach hurdles they must jump through upon deciding to conducting research on this topic. In these studies, scientists were able to perform the experiments easier due to mice being utilized as well as human subjects who already suffered from a gastrointestinal disease where FMT would benefit them.

When selecting articles for this study, the three mentioned were selected based on similarity to the research question as well as how recently they were published. Despite each study having their own minor flaws, the large pool of data that was synthesized is highly suggestive that FMT does indeed have the potential to alter brain chemistry, leading to positive mental health changes.

Many articles that did not meet the standards to be used in this study either due to year published, subjects used, or observation methods, despite their flaws, seemed to all come to the same conclusion. For this reason, the findings that came out of this were expected, with no surprising pieces of evidence that suggest conflicting data. The studies all came to the conclusion

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that performing a FMT from a donor with no history of mental health issues to a recipient that suffers from a mental health diagnosis, will in turn alter the recipient's gut bacterial flora and alleviate the negative mental health symptoms the subject is experiencing.

In the first study, The effect of fecal microbiota transplantation on psychiatric symptoms among subjects with irritable bowel syndrome, functional diarrhea and functional constipation: An open-label observational study, from the *Journal of Affective Disorders*, it was suggested that depression and anxiety symptoms may be improved by FMT regardless of gastrointestinal symptom change in patients with IBS, FDr and FC. This may be due to the increase of microbiota diversity that helps to improve patient's mood (Kurokawa et al., 2018).

In the second study, Transferring the blues: Depression-associated gut microbiota induces neuro-behavioral changes in the rat, from the *Journal of Psychiatric Research* it was discovered that FMT from depressed patients to microbiota-depleted rats induced behavioral and physiological features characteristic of depression in the recipient animal. This included anhedonia, anxiety like behaviors, and alterations in tryptophan metabolism. They discovered that the gut microbiota may play a causal role in the development of features of depression and may provide a tractable target in the treatment and prevention of this disorder (Kelly et al., 2016).

In the final study, Gut microbiome remodeling induces depressive-like behaviors through a pathway mediated by the host's metabolism from *Molecular Psychiatry*, it was found that the composition of gut microbiota is significantly altered in MDD patients compared to healthy controls and that this composition is transmissible. Colonization of GF mice with depression microbiota resulted in increased depression-like behaviors as compared with colonization with healthy microbiota (Zheng et al., 2016).



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The discovery of this medical milestone has the potential to have profound implications for the future of psychiatric treatments. Once widely available, this can become an available alternative for patients who are fed up with trying medication after medication only to experience undesirable side effects and no significant improvement of their actual symptoms.

This discovery could even start to become utilized for things beyond mental health. The gut-brain-axis has been assumed for quite some time, but the emergence of more solid data in recent years could mean bigger things for medicine. With more promising studies and results, FMT could revolutionize treatments for everything from psychiatrics, gastrointestinal, respiratory, cardiac, and on.

There is no doubt that FMT for the use of mental health disorders requires further research and trials. The available data suggests that there is a link between the gut microbiome and mental health and that this gut flora can be transferred person to person. The recipient who suffers from a mental health disorder can use the healthy donors transplant and alter their gut flora. Theoretically, this will result in a shift in thoughts, behaviors, and mindset.

With 7.1% of US Americans suffering from either anxiety or depression or having suffered from a major depressive disorder (NIH, 2019), alternative methods that suggest improvement in these illnesses must be further studied in an effort to improve the quality of life of these individuals. All three of the studies discussed reported an improvement in psychiatric symptoms through increase in microbiota diversity that is suggested to be transmissible. Although these three studies yielded optimistic and exciting results, one needs to keep in mind that three studies by no means can be representative of every FMT performed for the sole purpose of mental health improvement. There is always a possibility of perforation, introduction of a pathogen, undesirable GI symptoms, the potential to transfer other characteristics, and non-

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compliance with follow up resulting in further complications. For this reason, extensive research must continue to be done with human participants, large subject size, detailed screening of all candidates who participate. With further studies in the future involving psychiatric patients and beyond, FMT can be a promising alternative for many individuals who are refractory to years of medications and searching to regain their life back.

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