

The Comparison between the Effect of the Brain-Gut Axis and Traditional Medicine Treatment on Anxiety and Depression

Zichen Liu *

University of Wisconsin–Madison, WI, United States

* Corresponding author: zliu2223@wisc.edu

Abstract. Depression and Anxiety disorders are the two most prevail mental health conditions, and their proportion among people is growing year by year. Majority Anxiety disorders are generalized anxiety disorder (GAD), panic disorder, and social anxiety disorder (SAD). The gut-brain-micro biome (BGM) axis is an emerging area of research that studies two-way communication between the gut micro-biome and the brain. Studies have shown that the BGM axis can affect stress response, anxiety and depression. Interventions in the BGM axis, through probiotics such as Lactobacillus, have some benefits for anxiety and related disorders such as Hyperuricemia. This article briefly describes the different types of anxiety disorders, and discusses the diagnostic criteria, symptoms, morbidity and treatment options for each disorder. It highlights the current state of research on anxiety disorders, with emphasis on genetics, neuroimaging, and the gut-brain-microbiome (BGM) axis. Potential areas for further research and development of new therapeutic approaches were highlighted.

Keywords: GAD, SAD, gut-brain-micro biome (BGM) axis.

1. Introduction

In modern society, mental health issues that were once uncommon are now prevalent, with anxiety and depression being two of the most widespread conditions. Recent studies have shown that these conditions have been increasing across all demographic groups, albeit with varying magnitudes of increase. For instance, anxiety has been increasing the most from 30 to 44-year-olds, whereas depression metal disease has been increasing the most from 18 to 29-year-olds [1]. Furthermore, some researchers have found that some groups, such as Asian families in US with their children at home, have experienced a more pronounced increase in anxiety and depression. Moreover, people with lower education and income levels, as well as the unemployed, have a higher prevalence of anxiety and depression (as shown in fig 1). These findings indicate a pressing need for effective interventions that target vulnerable populations and address the mounting burden of anxiety and depression.

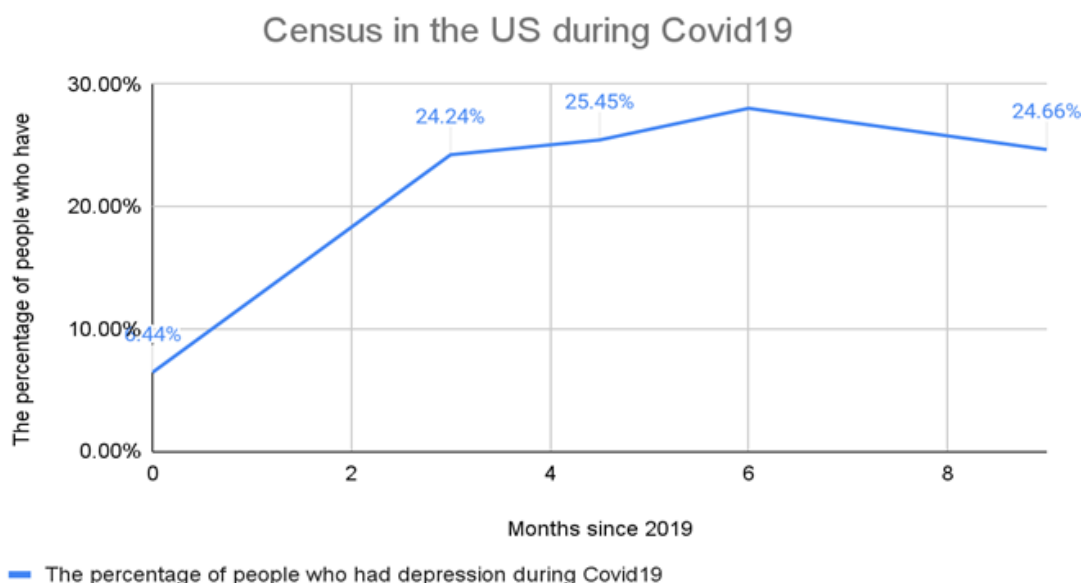


Figure 1. The percentage of people who had depression during Covid 19.

2. Anxiety Disorder and Depression

2.1. Information About Anxiety Disorder

2.1.1. The Definition of Anxiety Disorder

Fear and anxiety are complex emotions that have varying definitions depending on the context. According to Barlow's concept, anxiety is a mood that prepares for potential negative events in the future, on the other hand, fear is a quick alarm response to imminent danger, real or sensed, in the surrounding. Characteristics of anxiety include avoidance, worry, and muscle tension, however characteristics of fear include nausea, heart palpitations, trembling, sweating, and thoughts of imminent threat. Research shows that self-reported subjective symptoms affected by anxiety is different than self-reported somatic-visceral symptoms affected by fear. The tripartite model of fear, anxiety, and depression suggests that anhedonia and the absence of positive affect are respond to depression, while physiological hyper-arousal symptoms are related to fear. Subjective anxiety conditions are typically key markers of general distress. Even though these elements are distinct from each other, they are often normally to highly correlated [2]. There are many types of anxiety disorders, but major three are generalized anxiety disorder, panic disorder and social anxiety disorder.

2.1.2. Generalized Anxiety Disorder

Generalized anxiety disorder (GAD) is a diagnosis that came into existence in the 1980s after anxiety neurosis was distinguished from panic disorder. It is characterized by continuous senses of fearfulness that are considered as free-floating anxiety. While some clinicians argue that the diagnosis of GAD is ill-defined and has solid overlap with other disorders, also called comorbidity, it is still approved by clinical psycho-pharmacologists and epidemiologists. Advocates contend that it represents a step forward from earlier classifications, and its heightened occurrence in later stages of life distinguishes it from other anxiety disorders, signaling its permanence. GAD's diagnostic criteria have changed over time, with the current criteria requiring general and tenacious excessive anxiety, a combination of various somatic complaints and psychological, and a 6-month duration. One symptom of autonomic arousal is necessary for the diagnosis, along with up to three other symptoms such as fatigue, difficulty to focus, irritability, sleep deprivation, and physical tension. The DSM-IV criteria include the further symptom of worry over unimportant things, which distinguishes GAD from other disorders that involve specific anxious symptoms. Comorbidity associated with GAD is responsible for a significant amount of disability and morbidity, with social peer pressure, and economic burdens like depression. Clinicians have varying opinions on the usefulness of the diagnosis, but its increasing prevalence suggests that it will continue to be a diagnosis in the future [3].

2.1.3. Panic Disorder

Panic disorder is a complex anxiety disorder that is believed to have multiple genetic forms, with each form having a different group of genes or reflecting a wide vulnerability to anxiety or panic. The disorder is characterized by recurrent panic attacks occurred with physical characteristics such as otoneurological, cardiorespiratory, gastrointestinal, and autonomic symptoms. Panic disorder may occur in individuals who have been exposed to stress and trauma, such as those in military contexts.

Several genes have been implicated in panic disorder, including the adenosine 2A receptor gene and the cholecystokinin-B receptor gene. However, association researches of genes in neurotransmitter systems influenced by fear and anxiety have caused inconsistent and often non-replicated results. Neural circuitry changes have been observed in individuals with panic disorder, including reductions in temporal lobe volumes and amygdala and, decreased levels of phosphocreatine metabolites and creatine and in the medial temporal lobe, and lower cerebral glucose metabolism in regions such as the hippocampus, amygdala, brain-stem, and thalamus areas.

To be diagnosed with panic disorder, a person must encounter repeated instances of panic attacks and show behavioral changes or phobic avoidance because of these attacks. Panic disorder is often

accompanied by agoraphobia, an extreme form of phobic avoidance. It is necessary to note that not all panic attacks are suggesting panic disorder, as the same cognitive symptom and physical constellation can occur in a population with specific phobias or social phobia. Treatment and management of panic disorder involve psychotherapy, medication, or a combination of both [4].

2.1.4. Social Anxiety Disorder

Social anxiety disorder (SAD) is a phobic disorder that causes fear and prevention of social situations caused by the fear of embarrassment or humiliation. It is more prevalent in females, affecting 7.1% of people in a 12-month period and 12.1% of people over their lifetime. Patients experience fierce physical or emotional responses like fear, heart racing, sweating, and trembling when interacting with others, and the disorder can have a significant impact on their lives, leading to days of work lost. Treatment options include behavior therapy, cognitive therapy, pharmacotherapy, and psychotherapy, but diagnosing SAD can be challenging as it can resemble other disorders such as panic disorder, agoraphobia, depression, schizophrenia, bipolar disorder, or eating disorders. To resolve the diagnostic dilemma, practitioners should inquire about the cognitions and physical symptoms experienced by the patient during or in anticipation of their anxiety symptoms. Studies on the epidemiology, genetics, neuroimaging, and treatment of SAD have shown that chromosome 16 is involved in a region close to the candidate gene, the norepinephrine transporter. PET studies have also manifested changes in striatal dopaminergic function in patients with generalized SAD, and the amygdala and the insular cortex are parts of the brain that play a necessary part in the response to fear, with their activation correlating with the severances of social anxiety conditions. Although the causes and pathogenesis of SAD remain unclear, research continues to provide insight into its diagnosis, treatment, and underlying genetic and neurological mechanisms [5].

2.2. Depression

Depression is a mental illness that can impact people of any age and affect their quality of life. The condition may even lead to suicidal ideation. The development of drugs that prevent the deactivation of neurotransmitters in the brain has improved the treatment of depression. Two classes of antidepressant drugs, monoamine oxidase inhibitors and monoamine reuptake blockers, are available. Electroconvulsive therapy (ECT) is a last resort for severely depressed individuals who do not respond to conventional drug therapy. Recent research suggests that antidepressants and ECT work by increasing the production of neurotrophic factors in the brain. These factors may be deficient in people with depression. Neurotrophins are growth factors that support the function and growth of neurons containing 5-HT in the adult brain. Studies have shown that infusions of brain-derived neurotrophic factor (BDNF) and neurotrophin-3 (NT-3) into the rat midbrain increase the change of 5-HT and the concentration of noradrenaline in various forebrain regions. Infusions of BDNF or NT-3 also promote the reconstruction of serotonergic nerve fibers. Individuals with major depression have demonstrated decreased brain 5-HT turnover, and treatment with antidepressants boosts BDNF mRNA levels in the rat hippocampus. Therefore, a pharmacotherapy that raises neurotrophin production might be necessary to achieve a clinical response in depression, requiring nerve growth [6].

3. Brain-Gut Axis

The emerging field of study on the gut-brain-microbiome (BGM) involves animal models to acknowledge the relationship between the brain and the gut microbiota. This is accomplished through various techniques, such as manipulating the gut microbiota with antibiotics, fecal microbial transplantation, synthetic or human microbiota colonization, probiotics, and germ-free animal models. Researchers have made significant progress in understanding how the absence of common gut microbiota in early life can affect stress responsiveness in adulthood and how conventional microbiota can partially reverse these changes. The gut microbiota has been implicated in numerous

behaviors and conditions, such as depression-like and anxiety-like behavior, feeding behavior, nociceptive response, metabolic consequences and taste preference.

The gut microbiota triggers the central nervous system primarily completed by neuroimmune and neuroendocrine pathways, facilitated by microbial metabolites such as secondary bile acids (2BAs), short-chain fatty acids (SCFAs), and tryptophan metabolites. Some of these molecules can pass the intestinal barrier and enter systemic circulation, potentially crossing the blood-brain barrier. However, the gut-brain-microbiome (BGM) axis is limited by two natural barriers, the intestinal barrier, and the blood-brain barrier (BBB), which regulate molecular traffic between the cerebrospinal fluid of the CNS and the circulatory system.

The gut microbiota can up-regulate the expression of tight junction proteins, which decreases BBB permeability. The autonomic nervous network and CNS regulates gut functions, affecting the microbial habitat and modulating microbiota activity and composition. Stress can change the community structure of the gut microbiome and induce epithelial barrier defects, generating a pro-inflammatory environment in the gut.

In conclusion, the gut-brain-microbiome axis is a complex relationship influenced by various factors such as stress, diet, and circadian rhythm. While there is still much to learn, the gut microbiota is emerging as an influential factor in anxiety, depression, pain, and other neurological conditions. Understanding this axis may lead to novel therapeutic strategies for these conditions [7].

3.1. Different Bacteria

3.1.1. *Lacticaseibacillus paracasei*

In a recent study, researchers have discovered a bacterial strain, *Lactobacillus paracasei* NK112, that may have therapeutic potential for treating cognitive impairment, anxiety, and depression. This strain was isolated from human fecal microbiota and found to inhibit the expression of inflammatory cytokines, such as IL-6 and TNF-alpha, in macrophages that were stimulated with LPS. Additionally, NK112 was shown to reduce neuroinflammation by suppressing the expression of IL-6, IL-1beta, and TNF-alpha in the hippocampus, while increasing the expression of BDNF, a protein linked to psychiatric disorders.

Oral administration of NK112 was found to enhance cognitive function and alleviate depression- and anxiety-like behaviors in mice that were exposed to *Escherichia coli* K1. NK112 also decreased IL-6 levels in the hippocampus and corticosterone and IL-6 levels in the blood. The study suggests that NK112 has anti-inflammatory and neuroprotective effects, making it a promising candidate for treating neuroinflammatory and psychiatric disorders.

Stressors can induce neuroinflammation and suppress BDNF expression in mice, while cortisol and cytokine expression are closely associated with depression. NK112 was found to alleviate gut dysbiosis in mice induced by *Escherichia coli*, leading to improvements in gut microbiota composition. Further research is required to investigate the underlying mechanisms of these effects and to evaluate the safety and effectiveness of NK112 in clinical trials. Overall, this study highlights the potential of NK112 as a promising therapeutic agent for the treatment of cognitive impairment, anxiety, and depression [8].

3.1.2. *Lacticaseibacillus rhamnosus* Fmb14

High concentration of uric acid in the bloodstream can cause hyperuricemia, a metabolic disorder that can lead to serious health conditions like chronic kidney disease and gout. The commonness of hyperuricemia and gout has increased worldwide due to poor diet and lifestyle choices. Traditional treatments have limitations caused by high spending, adverse effects, and potential alterations to gut microbiota. Probiotics, with their long safety history and alleviative influence on metabolic syndromes, could be a promising strategy for preventing and treating hyperuricemia and related diseases.

Research has shown that hyperuricemia can cause gut microbiota dysbiosis, which can be improved with probiotic intervention. Probiotics play a vital factor in protecting kidney and the gut.

Lactobacillus has been found to decrease purine take in and improve intestinal epithelial barrier function. Probiotics promote the degradation of purine and enhance the expression of ATP binding cassette subfamily G member 2 (ABCG2) to increase uric acid secretion in the gut. Therefore, probiotic intervention could be a promising strategy for preventing and treating hyperuricemia and its related diseases.

This research investigated the ability of 11 lactic acid bacteria to degrade uric acid and purines and identified three strains with significant degradation abilities. In animal experiments, one of the strains, *L. rhamnosus* Fmb14, was found to decrease serum uric acid levels in hyperuricemia-induced mice by 36.8% compared to the model group. Fmb14 was found to downregulate XOD content to inhibit uric acid biosynthesis and increase the levels of ABCG2 in the colon. This study identified *L. rhamnosus* Fmb14 as a promising strain for further research into hyperuricemia prevention and treatment.

The study also investigated the impact of a high-purine diet-induced hyperuricemia on gut microbiota diversity and abundance in mice and the effect of administering Fmb14. The research found that hyperuricemia changed the structure of the gut microbiota by increasing Firmicutes and decreasing Bacteroidetes and Proteobacteria. Fmb14 treatment restored the gut microbiota's altered abundance due to a high-purine diet. Additionally, hyperuricemia was shown to affect metabolic functions by predicting metabolic pathways. Overall, the study concluded that Fmb14 has a positive effect on gut microbiota, and hyperuricemia enormously influenced the arrangement of the intestinal flora [9].

3.2. Selective Serotonin Reuptake Inhibitor

Selective serotonin reuptake inhibitors (SSRIs) have become a widely used class of medication for the treatment of depression. They work by regulating the amount of serotonin in the CNS, which is known to have a huge impact in the development and treatment of clinical depression. SSRIs are also used to treat a range of psychological disorders like obsessive-compulsive disorder, panic disorder, alcoholism, anxiety, migraine headache syndromes, chronic pain, and obesity. Some examples of SSRIs involve citalopram (Celexa), fluvoxamine (Luvox), escitalopram (Lexapro), paroxetine (Paxil), fluoxetine (Prozac), and sertraline (Zoloft). Reconcile is the first veterinary SSRI approved for canine behavioral issues, particularly separation anxiety.

Despite their widespread use, little information exists regarding the lowest acute dosage of any SSRI. However, it has been established that SSRIs have a broad boundary of safety, especially when compared to monoamine oxidase inhibitors and tricyclic antidepressants. Doses higher than five times the minimum adult therapeutic dose of a certain SSRI warrant referral to an emergency room. In animals, limited data are available regarding the use of SSRIs, despite lethal doses for some of the drugs have been discovered. For instance, the median toxic dose for fluoxetine in dogs is higher than 100 mg/kg, while citalopram is considered the SSRI with the biggest potential for toxicity in humans.

This paper discusses the current understanding of SSRIs, its mechanism of treatment, pathophysiology, toxic dose, clinical signs, action and prognosis for affected animals [10].

3.3. Comparison the *Lactobacillus paracasei*, Fmb14 and SSRIs

The first source provides a detailed analysis of the interaction between genetic regulations and environmental impacts in anxiety disorder and depression. The author compares drug treatment with the brain-gut axis as possible solutions. Exposure to environmental factors like noise and air pollution has been linked to an increased risk of anxiety. Traffic noise and NO_x levels have been found to contribute to both annoyance and anxiety. Alcohol consumption has also been studied as a potential factor, but its relationship with anxiety remains unclear. While pharmacotherapy, psychotherapy, and complementary medicine methods like phytotherapy are all available treatments for anxiety disorder, each has its own limitations and potential side effects. Selective serotonin reuptake inhibitors (SSRIs) and benzodiazepines are commonly used pharmacological treatments, but their long-term effectiveness is questionable. Combining pharmacotherapy with phytotherapy is suggested to

improve anxiety disorder and depression. Additionally, the author proposes the brain-gut axis as a potential therapeutic target for these conditions [11].

The use of selective serotonin reuptake inhibitors (SSRIs) for treating patients with depression and cardiac disease has been studied in several clinical trials. These trials have found that SSRIs, such as paroxetine, sertraline, and citalopram, have no significant adverse effects on cardiovascular function, such as blood pressure, cardiac conduction, or QT interval. Moreover, the cardiovascular safety of sertraline was confirmed in a large randomized clinical trial in patients with acute ischemic heart disease. However, SSRIs may have drug-drug interactions with cardiovascular medications due to inhibition of hepatic cytochrome P450 enzymes or protein-binding displacement. On the other hand, the serotonin-norepinephrine reuptake inhibitor, venlafaxine, is associated with a small increase in average heart rate and a dose-dependent increase in blood pressure. Elevated blood pressure associated with venlafaxine was significant only at doses above 225 mg/d and in groups at higher risk, such as older patients, men, and inpatients. Therefore, it is essential to consider the potential adverse effects and drug-drug interactions of antidepressants before prescribing them to patients with depression and cardiac disease [12].

The association between gut microbiota dysbiosis and mood disorders such as major depressive disorder (MDD) and bipolar disorder (BD) has been gaining increasing attention. The gut-brain axis, a communication pathway between the gut and the brain, is responsible for influencing the host's psychological state and brain function. Several human studies have identified changes in gut microbiota composition, including lower counts of lactobacilli and bifidobacteria in the gut microbiota of patients with MDD. Probiotics containing lactobacilli and bifidobacterial strains have been tested in human trials to control anxiety and depression with limited efficacy.

This single-arm trial evaluated the possible efficacy of *Lactocaseibacillus paracasei* strain Shirota (LcS), a widely used probiotic strain, in alleviating depressive symptoms in patients with MDD or BD. The study assessed changes in psychiatric symptoms over a 12-week period, analyzed gut microbiota composition and biological markers for intestinal permeability and inflammation, and searched for variables related to treatment outcomes. Participants were rated for depressive symptoms using the Hamilton Depression Rating Scale, 21-item version, and most participants were receiving psychotropic medications. LcS fermented milk containing at least 4.0×10^{10} colony-forming units (CFU) was administered to participants daily for 12 weeks.

The study enrolled 22 subjects, but two were excluded due to withdrawal of informed consent, leaving 20 subjects who completed the study. The total score of the Hamilton Rating Scale for Depression (HAM-D21) decreased significantly over the 12-week intervention period, while the score of the Beck Depression Inventory (BDI) tended to decrease, but the change was not statistically significant. The score of the Pittsburgh Sleep Quality Index (PSQI) decreased significantly over the study period, while there was no significant change in the Gastrointestinal Symptom Rating Scale (GSRS) total score or its subscales. The counts of total lactobacilli increased significantly after the intervention began, and *Lactocaseibacillus* was observed to be a significant component contributing to the increase [13].

In conclusion, this study suggests that daily intake of a probiotic supplement containing *Lactobacillus gasseri*, *Bifidobacterium bifidum*, and *Bifidobacterium longum* can improve depressive symptoms, sleep quality, and increase the counts of total lactobacilli in the gut microbiota. However, further studies with a larger sample size and longer intervention period are needed to confirm these findings.

The last academic article discusses the potential of probiotics, specifically *Lactobacillus rhamnosus* Fmb14, in treating inflammatory bowel disease (IBD) and associated mental disorders such as anxiety and depression. The article provides insight into the complex risk factors involved in IBD and the bidirectional role of the brain-gut axis in the pathogenesis of colitis-induced behavioral disorders. The article details the beneficial effects of probiotics on psychiatric and neurological disorders in animal models and highlights specific strains of probiotics, such as *Bifidobacterium*

longum and Lactobacillus acidophilus, that have been shown to improve mood disorders and cognition by regulating gut metabolism systems.

The study examined the therapeutic potential of Lactobacillus rhamnosus Fmb14 on mice with induced IBD. The researchers found that Fmb14 reduced hyperuricemia and body weight loss, improved organ index and serum cytokines, decreased levels of pro-inflammatory cytokines and increased levels of antioxidants. The study concluded that Fmb14 has the potential to alleviate IBD symptoms by reducing inflammation and oxidative stress and improving gut microbiota. The study also investigated the effect of Fmb14 on gut barrier function and found that Fmb14 treatment increased the expression of tight junction proteins, which were reduced by IBD exposure, suggesting that Fmb14 can improve colonic inflammation and gut barrier function by regulating cytokines, oxidative stress, and tight junction proteins, which could be used as a potential therapeutic agent for colitis. Overall, the article provides valuable insights into the potential of probiotics in treating IBD and associated mental disorders, highlighting specific strains and mechanisms of action [14].

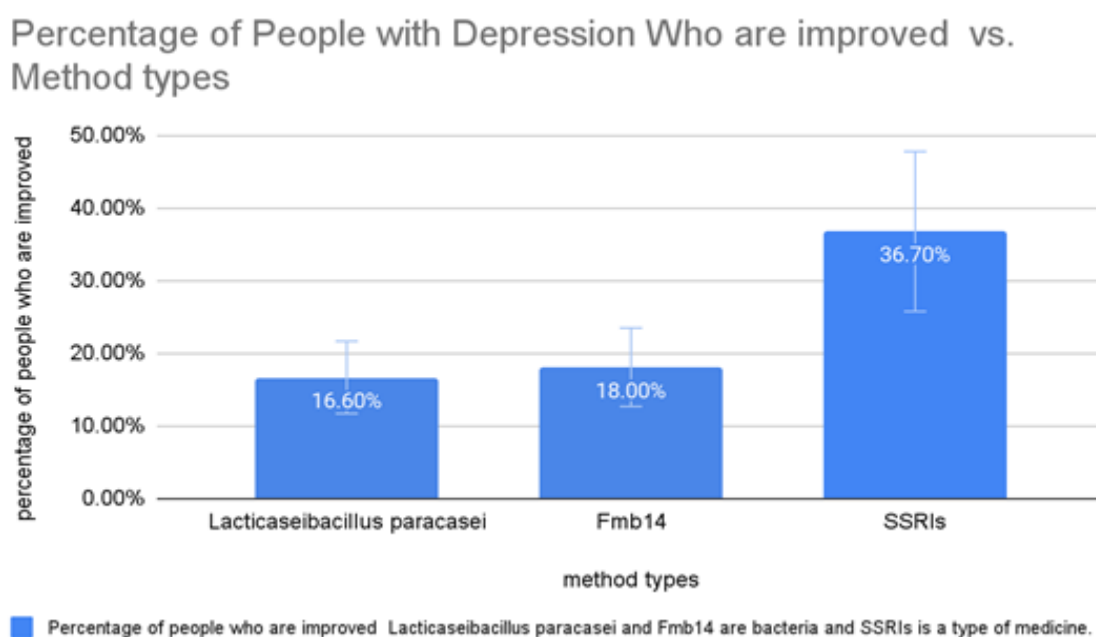


Figure 2. The graph shows the percentage of people during 7 days with different treatments who were improved with their depression condition. The error bars and the percentage are shown on this graph [12-14]

The results from these three comparisons are very apparent. The time period for these experiments is 7 days and there is no significant difference between lacticaseibacillus paracasei and Fmb14. They both shows approximately half percents, of people who are improved by these treatments, of SSRIs. Although those researchers use different methods to conduct this result, the overall effectiveness can suggest some references. To found a scale of depression for those patients also faces difficulty. Additionally, the side-effects of having over-dose lacticaseibacillus paracasei and Fmb14 are remain undisclosed.

4. Conclusion

In summary, fear and anxiety are intricate emotions that are fundamental to human survival. The connection between the gastrointestinal tract and nervous system is bidirectional and is influenced by a variety of factors. It is crucial to comprehend the underlying mechanisms to understand the pathophysiology of functional GI diseases. While research in rodents has provided significant proof, it is essential to apply these findings to humans to identify potential treatment options. Using machine learning algorithms, pathogenic microbiome signatures, together with demographic, serological, and neuroimaging data, can be analyzed to reveal previously unnoticed trends and patterns. This attempt

has the potential to unlock new insights into the relationship between fear, anxiety, and the gut-brain axis, which could ultimately lead to the development of more effective therapies for functional GI diseases. Research studies have focused on understanding the epidemiology, genetics, neuroimaging, and treatment of anxiety disorders. The brain-gut-microbiome axis is an emerging area of research that highlights the importance of the gut microbiota in regulating stress responsiveness, depression-like or anxiety-like behavior, and metabolic consequences. Probiotics, such as *Lactobacillus*, have shown promising results in improving gut microbiota composition and alleviating symptoms of anxiety and depression in animal studies. *Lacticaseibacillus rhamnosus* Fmb14 may also hold potential in preventing and treating hyperuricemia and related diseases. Overall, continued research is necessary to better recognize the complicated mechanisms underlying anxiety disorders and the hidden characteristics of the brain-gut axis in their growth and treatment. The findings from these studies may help develop more effective therapies for patients with anxiety disorders and improve their overall quality of life.

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