Effect of Fecal Microbiota Transplant on Symptoms of Psychiatric Disorders: A Systematic Review

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Abstract
Background: The Gut-Brain-Axis is a bidirectional signaling pathway between the gastrointestinal (GI) tract and the brain. The hundreds of trillions of microorganisms populating the gastrointestinal tract are thought to modulate this connection, and have far reaching effects on the immune system, central and autonomic nervous systems, and GI functioning. These interactions have also been linked to various psychiatric illnesses such as depression, anxiety, substance abuse, and eating disorders. It is hypothesized that techniques aimed at strengthening and repopulating the gut microbiome, such as Fecal Microbiota Transplant (FMT), may be useful in the prevention and treatment of psychiatric illnesses.

Methods: A systematic search of five databases was conducted using key terms related to FMT and psychiatric illnesses. All results were then evaluated based on specific eligibility criteria.

Results: Twenty-one studies met the eligibility criteria and were analysed for reported changes in mood and behavioural measures indicative of psychiatric wellbeing. The studies included were either entirely clinical (n=7), preclinical with human donors (n=7), or entirely preclinical (n=7). All studies found a decrease in depressive and anxiety-like symptoms and behaviours resulting from the transplantation of healthy microbiota. The inverse was also found, with the transmission of depressive and anxiety-like symptoms and behaviours resulting from the transplantation of microbiota from psychiatrically ill donors to healthy recipients.

Conclusion: There appears to be strong evidence for the treatment and transmission of psychiatric illnesses through FMT. Further research with larger sample sizes and stronger scientific design is warranted in order to fully determine the efficacy and safety of this potential treatment.

Background
In recent years, there has been a growing appreciation for research in the field of the “gut-brain axis” (GBA). The GBA consists of bidirectional biochemical and neural signalling between the gastrointestinal (GI) tract and the brain. Specifically, the gut microbiota is able to modulate the GBA both directly and indirectly via endocrine, neural, and immune pathways. In disease- or stress-states these pathways may become compromised resulting in intestinal dysbiosis, changes in mood,
behavior, and cognition, and altered inflammatory levels (Cryan & Dinan, 2012).

The gastrointestinal tract is colonized by over one hundred trillion commensal bacteria that exist symbiotically with our bodies. Colonization of the gut occurs at birth and is largely influenced by mode of delivery (c-section vs. vaginal birth) and through breast feeding. However, bacterial composition of the gut begins to stabilize throughout adulthood (Martin et al., 2016). Detailed analyses of human gut microbiota have shown considerable individual variability in bacterial content as this dynamic system is influenced by a variety of factors, such as genetics, diet, metabolism, age, geography, antibiotic treatment, and stress (Foster & McVey Neufeld, 2013).

Gut microbiota are critical in the normal development of the immune system, central nervous system (CNS) circuitry, GI functioning, and autonomic nervous system (ANS) functioning. This community of bacteria and its genetic material is often referred to as a virtual organ (Foster & McVey Neufeld, 2013; O’Hara & Shanahan, 2006; Zhu et al., 2010). Studies have since shown that gut bacteria play a vital role in regulating important aspects of brain development and function, along with other host physiology (O’Hara & Shanahan, 2006; Stilling et al., 2014).

The Gut and Psychiatric Symptoms and Disorders

The interaction of the gut with the environmental risk factors of psychiatric illnesses, such as diet and early life stress, suggests that interventions targeting the gut microbiome could prevent and treat psychiatric symptoms (Dash et al., 2015). Psychiatric symptoms can manifest in both psychological and physiological ways, often resulting in impaired functioning. Common physiological symptoms share similarities with symptoms of GI disorders, such as Irritable Bowel Syndrome (IBS). This association may be explained by the close connection between the gut and the brain.

In past studies, individuals with psychiatric illness have also been shown to have a dissimilar microbiota composition compared to healthy individuals, due to decreased diversity and abundance of the healthy gut microbes (Liu et al., 2016). Studies also show that lack of exposure to commensal bacteria, such as in germ-free mice, has significant effects on stress responsiveness in adulthood; it has also been shown that early colonization of the gut with a conventional microbiota, even a single species, can partially reverse these effects (Sudo et al., 2004). Some investigations have shown
neurochemical changes as a result of gut microbiome dysfunction, such as altered levels of brain-derived neurotropic factor (BDNF), reduced serotonin receptor expression, reduced synaptic plasticity gene expression, and increased striatal monoamine turnover (Heijtz et al., 2011; Neufeld et al., 2011; Sudo et al., 2004).

Fecal Microbiota Transplant
Several methods of examining the influence of the gut microbiome on the gut-brain axis have been explored, including manipulating the microbiome via probiotic and antibiotic administration, the use of germ-free animal models, and perhaps most notably, fecal microbiota transplantation (FMT). FMT is the transfer of fecal bacteria from a healthy donor to a recipient. FMT was first used in 4th century China for the treatment of severe food poisoning and diarrhea and other related symptoms (F. Zhang et al., 2012). However, it is currently only indicated for the treatment of Clostridium difficile (C. diff.) infections. C. diff is often contracted by older patients in-hospital following routine pharmacological treatments such as antibiotics. The use of antibiotics often depletes healthy bacteria in the GI tract which can result in microbial dysfunction. FMT is used to restore healthy status of the microbiome via repopulation of healthy bacteria to the gut. Functioning in a similar manner to probiotics, this treatment method helps to maintain the bacterial balance and function. FMT are most commonly accomplished via endoscopies, enemas, and oral feeding of freeze-dried material. Aside from GI and psychiatric disorders, this treatment method is also being explored as a potential treatment for metabolic disorders, autism, multiple sclerosis, and Parkinson’s disease (de Groot et al., 2017; H. Huang et al., 2019; Kang et al., 2017; Makkawi et al., 2018). Other variations of this treatment, such as Microbial Ecosystem Therapeutics-2 (MET-2) are also currently being explored, in psychiatric indications such as Generalized Anxiety (GAD) and Major Depressive Disorders (MDD). MET-2 consists of gut bacteria obtained from stool samples of a healthy donor, chosen for its safety profile, that is then purified and lab-grown prior to being lyophilized and ingested orally by patients (Chinna Meyyappan & Milev, 2019).

FMT in the Context of Psychiatric Illness
Two of the most prevalent groups of psychiatric disorders include Major Depressive Disorder and
anxiety disorders. MDD is characterized by either depressed mood and/or loss of interest or pleasure, as well other psychiatric and physiological symptoms. Anxiety disorders is a category that includes a variety of disorders characterized by intense feelings of anxiety, nervousness, or fear. These include Generalized Anxiety Disorder, Agoraphobia, Panic Disorder, and specific phobias. Both groups of disorders are characterized by a significant impairment in daily functioning (American Psychiatric Association, 2013). While there are pharmacological treatments available for both disorders, many people deny treatment due to side effects or stigma-related reasons or are treatment-resistant and unable to find an effective way to improve their symptoms. By targeting the gut, FMT may be a potential way to overcome these drawbacks. Research on the gut-brain axis indicates that there may be a possibility to improve these symptoms through restoration of the gut microbiome via fecal transplant from a healthy donor. However, as this is a relatively novel area of research, there are few studies on FMT in humans as a treatment method in the context of psychiatric disorders. This review examines findings from preclinical and clinical studies that have examined the effects of endogenous microbiome transfer on psychiatric symptoms. The studies included in this review assess the effects of FMT and related interventions on symptoms associated with a variety of psychiatric illnesses including MDD, anxiety, and chronic stress. Comorbid disorders associated with poor mental health outcomes such as alcoholism and anorexia were also included in several of the studies.

Methods

Literature Search Strategy

This review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Fig. 1, Moher et al. 2009). Relevant studies were identified by systematically searching the following databases: MEDLINE, EMBASE, CINAHL, PsycINFO, and Web of Science using key search terms including: mood, anxiety, mania, stress, phobia, microbiota transfer, and fecal transplant. The strategy adapted to each of the databases listed above and is described in detail in Appendix 1. Searches were conducted in November 2019 and yielded 285 studies after duplicates were removed.

Eligibility Criteria

All articles eligible for inclusion were published in peer-reviewed journals and were written in English.
The studies were restricted to preclinical or clinical samples that were assessed for changes in symptoms of psychiatric illness after undergoing an endogenous microbe transfer via any route of administration.

**Study Selection**

One author (A.C.M) completed initial search of the databases, adhering to the search strategy (Appendix 1). Two authors (A.C.M and C.W) independently assessed the titles and abstracts of records retrieved from the systematic search according to the identified inclusion and exclusion criteria and completed the full-text review. Any disagreements were resolved by a third author (R.M).

**Study Quality**

The Cochrane Handbook for Systematic Reviews of Interventions Risk of Bias Tool (RoBT) addresses 6 specific domains in assessing the quality of randomized controlled trials: sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting and ‘other issues’. All included studies were analyzed according to these domains by A.C.M and C.W. As there is limited research on this topic, studies that did not follow the double-blind, randomized controlled model, were included if they had a comprehensive methodology after thorough analysis by three of the authors (A.C.M., C.W., and R.M.). Overall, the included studies presented with low levels of potential bias. In cases where blinding of either participant or study team was not performed, bias was assessed as high. Detailed assessments can be found in Table 1. Allocation concealment was not assessed since no studies concealed treatment allocation from subjects or participants.

| Study      | Blinding of outcome assessors for All outcomes | Blinding of participants and personnel for All outcomes | Incomplete outcome data for All outcomes | Selective outcome reporting | Sequence Generation |
|------------|-----------------------------------------------|------------------------------------------------------|----------------------------------------|-----------------------------|---------------------|
|            | Judgement | Comments                                     | Judgement | Comments                                      | Judgement | Judgement | Judgement | Comments                                      |
| Cai 2019   | High      | Single outcome group, no blinding of any parties involved | High      | Single case, no blinding of any parties involved | Unclear   | Unclear   | High      | Single case, no sequence generation |
| Tillmann 2019 | Low        | Low                                            | Low       | Low                                           | Low       | Low       | Low       | |
| Kurokawa 2018 | High       | Outcome assessors were not blinded.             | High      | Participant’s and personnel were not blinded. | Low       | Low       | Low       | |
| Author Year   | Study Characteristics                                                                                                                                                                                                 | Low | Low | Low | Low |
|--------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----|-----|-----|-----|
| DePalma 2017 | Investigators were not blinded for behavioura l and gastrointestinal motility tests.                                                                                                                                  | Low | Low | Low | Low |
| Xiao 2018    |                                                                                                                                                                                                                       | Low | Low | Low | Low |
| Mazzawi 2018 | Outcomes assessors not blinded.                                                                                                                                                                                        | High| High| Low | Low |
| Xu 2018      | Participant s and personnel not blinded.                                                                                                                                                                                | Low | Low | Low | Low |
| Huang 2019   | Participant s and personnel not blinded.                                                                                                                                                                               | Low | Low | Low | Low |
| Huang 2019   | Outcomes assessors were not blinded.                                                                                                                                                                                    | High| High| Low | Low |
| Li 2019      | Participant s and personnel were not blinded.                                                                                                                                                                           | Low | Low | Low | Low |
| Zhang 2019   | Participant s and personnel were not blinded.                                                                                                                                                                           | Low | Low | Low | Low |
| Xie 2019     | Outcome assessors were not blinded.                                                                                                                                                                                     | High| High| Low | Low |
| Zhao 2019    |                                                                                                                                                                                                                       | Low | Low | Low | Low |
| Kelly 2016   |                                                                                                                                                                                                                       | Low | Low | Low | Low |
| Mizuno 2017  | Participant s and personnel were not blinded.                                                                                                                                                                           | Low | Low | Low | Low |
| Langgartner 2018 | Outcome assessors, aside from histological scoring, were not blinded.                                                                                           | High| High| Low | Low |
| Yang 2019    | Participant s and personnel were not blinded.                                                                                                                                                                           | Low | Low | Low | Low |
| Hata 2019    | Participant s and personnel were not blinded.                                                                                                                                                                           | Low | Low | Low | Low |
| Lv 2019      | Participant s and personnel were not blinded.                                                                                                                                                                           | Low | Low | Low | Low |
| Zheng 2016   | Participant s and personnel were not blinded.                                                                                                                                                                           | Low | Low | Low | Low |

Results

Study Characteristics

This review contains 21 studies evaluating the effect of fecal microbiota transplants on various psychiatric and physical symptoms. Of these, seven studies examined exclusively animal samples, seven studies were preclinical subjects with transplanted microbiota from human donors, and seven studies examined exclusively human samples. The characteristics of these studies are displayed in Tables 2, 3, and 4. The average sample size was n = 22 for entirely preclinical studies, and n = 93 for preclinical studies with human donors, and n = 10 for clinical studies. Four of the preclinical studies failed to report rodent sample size. The symptoms most frequently studied were that of Irritable
Bowel Syndrome (IBS), chronic stress, and depressive-like symptoms.

Table 2
Preclinical Studies

| Study | Sample Characteristics | Study Design | Intervention | Donor | Measurement | Key Findings and Conclusions |
|-------|------------------------|--------------|--------------|-------|-------------|------------------------------|
| Zhang et al., 2019 | Chronic Stress Mice | Randomized Controlled Trial | FMT from wildtype (WT) and NLRP3 KO mice to chronic unpredictable stress (CUS) mice | WT and NLRP3 KO mice | SPT, FST, TST, and OFT | Transplantation of the NLRP3 KO gut microbiota ameliorated CUS-induced depressive-like behaviors. |
| Li et al., 2019 | Antibiotic treated 8 male WT and 8 male chronic unpredictable mild stress (CUMS) mice | Randomized Controlled Trial | Oral FMT for 2 weeks from WT and CUMS mice to antibiotic-treated WT and CUMS mice | 8 WT mice and 8 CUMS mice | SPT, OFT, EPM, FST | FMT of CUMS microbiota induced anxiety-like and depression-like behavior in the recipient mice |
| Lv et al., 2019 | Antibiotic treated Male rats with and without CUS | Randomized Controlled Trial | 3-day oral FMT from WT and CUMS mice to antibiotic-treated rats with and without CUS | WT and CUMS mice | SPT, OFT, EPM, FST | Transplantation of CUMS Microbiome Induces Depression-Like Behaviors in Antibiotic-Treated Rats as shown via a decrease in time spent in the central area in the OFT and increased immobility in the TST |
| Xiao et al., 2018 | 6-8 week male C57BL/6 mice | Randomized Controlled Trial | 14 days of saline or oral FMT from alcohol or water exposed mice to healthy control mice | Alcohol-exposed and water-exposed mice | FST and TST | FMT from alcohol-exposed mice induced depressive behavior in the recipients, shown by significant results in FST and TST. Alcohol withdrawal induced symptoms were transmitted to healthy controls |
| Yang et al., 2019 | Antibiotic treated two-month-old male C57BL/6 mice | Randomized Controlled Trial | 14 days of FMT from rats to antibiotic treated C57BL/6 mice | Two-month old Sprague Dawley rats with and without anhedonia | Mechanical withdrawal test (MWT), Tail flick test (TFT), SPT, locomotion, TST, and FST | Antibiotic administration significantly aggravated the MWT scores, latency of TFT, and depression. |
| Study                          | Animals                          | Design                        | Intervention                                                                 | Outcomes                                                                 |
|-------------------------------|----------------------------------|-------------------------------|------------------------------------------------------------------------------|--------------------------------------------------------------------------|
| Tillmann et al., 2019         | 24 adult male Flinders sensitive line (FSL) and 24 Flinders resistant line | Randomized Controlled Trial   | FMT from FRL, saline, or FSL rats to FRL and FSL rats administered every third day over a 16-day period | OFT and FST                                                              |
|                               |                                  |                               | FSL, FRL, or saline rats                                                     | • Rats receiving FRL feces struggled less than saline-treated ones while there was no difference between FSL feces and saline or FSL and FRL feces.  
|                               |                                  |                               |                                                                              | • Rats receiving FSL feces had significantly increased immobility compared with saline, whereas FRL feces did not differ from saline.  
|                               |                                  |                               |                                                                              | • No difference in immobility between FSL and FRL feces.                 |
| Langgartner et al., 2018      | Male C57BL/6N chronically stressed mice via chronic subordinate colony (CSC) | Randomized Controlled Trial   | Repeated FMT from non-stressed single-housed control (SHC) mice              | OFT and open-field/novel object (OF/NO) test                                   |
|                               |                                  |                               | Non-stressed, SHC Male C57BL/6N mice                                         | • SHC feces transplantation had mild stress-protective effects as shown by an improvement of CSC-induced thymus atrophy, anxiety, systemic low-grade inflammation |

- FMT from rats with anhedonia significantly aggravated behavioral abnormalities, pain, depression-like, and anhedonia-like behaviors in recipient mice.
- Antibiotics-treated pseudogerm-free mice showed depression-like and anhedonia-like phenotype compared to control group, which were improved by FMT from mice without anhedonia.
Inflammation, and alterations in bone homeostasis. • CSC feces transplantation slightly aggravated CSC-induced systemic low-grade inflammation and alterations in bone homeostasis in SHC and/or CSC animals.

Table 3
Preclinical Studies with Human Donors

| Study            | Sample Characteristics | Study Design          | Intervention                                                                 | Donor                                | Measurement                                                      | Key Findings and Conclusions                                                                 |
|------------------|------------------------|-----------------------|------------------------------------------------------------------------------|--------------------------------------|------------------------------------------------------------------|---------------------------------------------------------------------------------------------|
| De Palma et al. 2019 | 141 GF NIH Swiss Mice  | Randomized Controlled Trial | FMT from IBS patients and healthy donors to GF mice | 4 Anxious IBS-D patients, 4 non-anxious IBS-D patients, Mean age: 40 years old; 5 healthy human controls (HHC), Mean age: 42 years | Donors: HAM-A Recipients: Light-dark preference test and step-down test | • FMT from anxious IBS-patients to mice produced anxiety behaviors in mice  
• FMT from IBS patients with normal anxiety and from healthy controls to GF mice showed no significant anxious behaviors in GF mice  
• Akkermansia was associated with anxiety behaviors in mice |
| Hata et al., 2019 | Germ-free (GF) BALB/c mice | Randomized Controlled Trial | Oral FMT with and without pre-treatment with live Bacteroides vulgatus to GF mice | 4 AN patients, Mean age: 23 years, BMI 13.7; 4 HHC, Mean age: 25.3 years, BMI 21.6 | Donors: DSM diagnosis of AN Recipients: Open Field and Marble Burying | • FMT from AN patients induces anxiety-like and compulsive behaviors in GF recipient mice and impairs body weight gain  
• Pre-treatment with B. vulgatus attenuates compulsive behavior |
| Zhao et al., 2019 | Male C57BL/6J mice with antibiotic gut microbiota suppression, 6 weeks old | Randomized Controlled Trial | FMT via intragastric administration every other day for 13 days to antibiotic | Patients with and without alcoholism, Ages 35–40 | Donors: ICD-10 diagnosis of alcoholism Recipients: Open field test (OFT), alcohol preference | • FMT from patients with alcoholism induced spontaneous alcohol dependence in |
antibiotic-treated mice

FMT from MDD patients and healthy controls to GF mice

5 MDD patients; 5 HHC

Donor: DSM-IV diagnosis of depression and HAM-D
Recipient: OFT, TST, forced swimming test (FST), buried food pellet test (BFP) and olfaction behavior test (via modified BFP)

FMT from MDD patients resulted in significantly increased immobility times for the FST and TST
• The center motion distance (OFT) also significantly decreased compared to controls
• The latency for finding the object by depressed mice was significantly longer than that by healthy controls indicating impaired olfaction.

Rats receiving FMT from MDD patients demonstrated anhedonia-like behaviours as shown by a significant decrease in sucrose intake without affecting fluid intake in SPT
• Rats receiving FMT from MDD patients also exhibited anxiety-like behaviours as shown by a significant decrease in visits to the open arms in the EMT and a reduction in time spent in the centre in the OFT.
• In the forced swim test, there were no significant
| Xu et al., 2018 | 110 male C57BL/6 mice aged 4 to 5 weeks exposed to chronic ethanol | Randomized Controlled Trial | FMT 1: FMT at the end of chronic alcohol exposure period  
FMT 2: FMT at middle (6%) of alcohol exposure period  
FMT 3: FMT at the beginning of whole exposure period | 3 HHC | Recipients: OFT, TST, FST, and APT |
| --- | --- | --- | --- | --- | --- |
| Xu et al., 2018 | Male GF Kunming mice and specific pathogen free (SPF) Kunming mice, 6–8 weeks old | Randomized Controlled Trial | Pooled sample FMT from MDD patients and HHC to GF mice | 5 Male MDD patients, ages 26–61; 5 Male HHC, ages 29–60 | Recipients: OFT, FST, TST |
| Zheng et al., 2016 | Male GF Kunming mice and specific pathogen free (SPF) Kunming mice, 6–8 weeks old | Randomized Controlled Trial | Pooled sample FMT from MDD patients and HHC to GF mice | 5 Male MDD patients, ages 26–61; 5 Male HHC, ages 29–60 | Recipients: OFT, FST, TST |
like behaviors compared to HC colonization
• Weight was not significantly different between groups

| Study | Sample Characteristics | Study Design | Intervention | Donor | Measurement | Key Findings and Conclusions |
|-------|-------------------------|--------------|--------------|-------|-------------|-----------------------------|
| Cai et al., 2019 | 1 female MDD patient, 79 years old | Pre- and post-intervention assessment | Single time FMT via gastroscope | 6 year-old grandson | PHQ-9 | Six months after intervention PHQ-9 scores improved. Significant increase in Firmicutes counts and Bacteroides significantly reduced |
| De Clerq et al., 2019 | 1 female AN patient, 26 years old | Case report, pre- and post-intervention assessment | Single duodenal FMT | Unrelated female donor with BMI of 25 | BMI, caloric intake | Increase in BMI post-intervention. No significant differences in gut microbiota composition after FMT |
| Huang et al., 2019 | 30 (18M, 12F) refractory IBS patients, Mean age: 44 years old | Pre- and post intervention assessment with 1, 3, and 6 month follow-ups | Two to three FMT procedures (done every other day) via colonoscopy | Healthy volunteers aged 8-35 | IBS-QOL, IBS-SSS, GSRS, HAM-A and HAM-D | Significantly improved GI symptoms and alleviated depression and anxiety as indicated by IBS-QOL, IBS-SSS, GSRS, HAM-A and HAM-D scores, 1 and 3 months post-FMT. Increase in Verrucomicrobia and Euryarchaeota at phyla level and increase in Methanobrevibacter and Akkermansia at the genus level, at 1 month after FMT compared to before FMT |
| Mazzawi et al. | 13 (9M, 4F) IBS patients, Mean age: 32 years old | Open label, pilot study | Single duodenal FMT via gastroscope | Healthy donors, aged 20-42 | IBS-SQ, IBS-SSS, EPQ-N-12, and HAD | Scores of all questionnaires improved significantly at all follow-up time points and lasted up to 28 weeks |
### Preclinical Studies

Of the seven preclinical studies included in this review (Table 2), the primary indication investigated was chronic stress in four of the studies, and alcoholism, depression and chronic neuropathic pain in...
the remaining three, respectively. Of the studies assessing chronic stress, two investigated the effects of FMT from mice subjected to the chronic unpredictable mild stress (CUMS) procedure to healthy mice, one investigated the effects of fecal transplant from healthy mice to stressed mice, and one investigated the effects of FMT from NLPR3 knockout mice on the resiliency of mice subjected to the CUMS procedure after fecal transplant. When investigating the effects of FMT from CUMS mice to germ free mice, two studies found that the FMT resulted in increased anxiety and depression-like behaviour (Li et al., 2019; Lv et al., 2019). Mice were assessed using the open-field, tail suspension, forced swimming, and elevated plus maze tests – all standard tests for evaluating symptoms related to stress and depression in the field of depression research in mice.

Langgartner et al. investigated the alleviating properties of FMT by designing a study in which mice were split into chronic subordinate colony housing (CSC) and non-stressful single housing (SHC). CSC housing is a validated way to subject mice to chronic psychological stress, similar to the CUMS procedure. The researchers then evaluated if frequent FMT from SHC to CSC mice could stop the development of anxiety and depression-like symptoms. It was found that these transplants were mildly stress protective, resulting in decreased anxiety and depression-like symptoms in the recipient mice (Langgartner et al., 2018). Zhang et al. also investigated the protective properties of FMT by transplanting the microbiota from NLPR3 knockout mice into GF mice. NLPR3 is a gene involved in the aforementioned immune pathway that modulates the GBA. The transcripts of this gene have been found to be increased in both patients with depression and mouse models for depression (Alcocer-Gómez et al., 2014, (Yi Zhang et al., 2014). Knocking out this gene is thought to be protective against the development of depressive-like symptoms in mice. These mice were then subjected to the CUMS procedure in order to see the effects of the FMT on their resiliency. It was found that FMT from NLPR3 knockout mice resulted in a decrease in anxiety and depressive-like behaviours in the recipient mice (Yuan Zhang et al., 2019).

Xio et al. evaluated the transfer of alcohol-withdrawal symptoms via FMT. In this study, the donor mice were treated with alcohol – they were forced to ingest alcohol for two weeks, with the concentration of alcohol increasing from 5-35% over that time period. The fecal microbiota of these
mice was then transplanted into healthy control mice. This transplantation resulted in depressive behaviour in the recipient mice. This behaviour was evaluated using the forced swim and tail suspension tests (Xiao et al., 2018). Additionally, Tillmann et al. also studied the use of FMT to transfer depressive behaviour, using a Flinders sensitive line (FSL) and Flinders resistant line (FRL) rats. FSL and FRL rats have been widely used for over 30 years as a depression model in rats (Overstreet & Wegener, 2013), where FSL rats display depressive-like behaviours, and FRL rats are resistant to the development of depressive-like behaviours. Tillman et al. investigated the effects of FMT from FSL and FRL rats to FSL, FRL and saline control groups. The only significant behavioural results found were an increased immobility in the forced swim test and decreased time spent in the centre of the open field test resulting from FMT from FSL to control rats, and that rats receiving FRL feces struggled less in the forced swim test than those receiving saline (Tillmann et al., 2019). The former suggests the transfer of depression symptoms from FSL rats to others, and the latter provides evidence against the transference of resiliency from FRL rats. Yang et al. measured pain and depression symptoms in mice after FMT from rats with neuropathic pain presenting with and without anhedonia. Rats were administered a spinal neuropathic injury (SNI) and then assessed for anhedonia susceptibility. After being separated into anhedonia-susceptible and resilient groups, the rats’ microbiota was then transplanted into mice, and the mice were assessed for pain responses and depression-like symptoms. It was found that transplants from anhedonia susceptible rats aggravated pain and depression-like symptoms, and those receiving from anhedonia resilient microbiotas had improved pain and depression-like symptoms.

Preclinical Studies with Human Donors

Of the seven preclinical studies performing FMT from human donors to germ free (GF) mice (Table 3), three assessed the effects of FMT from patients with depression, one from patients with alcoholism, one from patients with anorexia and one from patients with IBS. Lastly, one study assessed the transfer of gut microbiome from healthy human controls to mouse models of alcoholism. These mice were then assessed for changes in various tests used to indicate change in psychiatric state.

After FMT from individuals with depression to GF mice, all studies found a decrease in centre motion.
in the open field test. Two studies also found a significant increase in immobility duration in the tail suspension and forced swim tests (C. Huang et al., 2019; Zheng et al., 2016). Although Kelly et al. did not find any changes in the forced swim test, they found a decrease in the total visits to the open arms in the elevated plus maze (Kelly et al., 2016). These three studies all support that FMT from patients with depression to GF mice can result in depression-like behaviour in the recipient mice.

Alcoholism is highly comorbid with mood and anxiety disorders, with someone with alcoholism being 3.6 and 2.6 times more likely to have a mood or anxiety disorder respectively (Petrakis et al., 2002). In the studies investigating the effect of FMT on depressive and anxiety-like behaviors related to alcoholism, Zhao et al. found that transplants from patients with alcoholism to GF mice resulted in depression and anxiety-like behaviours in the aforementioned tests (Zhao et al., 2019). The inverse was conducted by Xu et al. – in their study, mice were treated with alcohol and as a result these mice displayed depression and anxiety-like symptoms in the same tests. FMT was then performed from healthy human donors at different time points throughout the alcohol treatment. Xu et al. found that when administering 3 FMTs per week, if the transplants began before or during the alcohol treatment, the depression and anxiety-like behaviours were not observed (Xu et al., 2018).

Anorexia is also closely tied to mood and anxiety disorders, with the likelihood of someone with anorexia having a comorbid mood or anxiety disorder being 2.4 and 1.9 times higher respectively than the general public (Hudson et al., 2007). When assessing the effects of FMT from patients with anorexia to germ free mice, Hata et al. observed an increase in compulsive and anxiety-like behaviours in the mice when assessed using the open field and marble burying test. As previously seen, the mice spent significantly less time in the centre of the open field test, suggesting anxiety-like behaviour. The mice also buried more marbles than control mice, suggesting compulsive behaviour. The mice also buried more marbles than control mice, suggesting compulsive behaviour (Hata et al., 2019). These findings are also consistent in De Palma et al.’s study where transfer of anxiety and IBS symptoms to GF mice via FMT was assessed. In their study, it was found that transplants from anxious IBS donors resulted in more anxiety-like behaviour in recipient mice. This was not the same for transplants from IBS donors without anxiety (De Palma et al., 2017). These studies all show that FMT
can confer certain traits of the donor’s psychiatric illnesses to the recipient mouse, and that transplants from healthy donors may be able to alleviate some psychiatric symptom.

Clinical Studies
In contrast to the preclinical studies with human donors, where transplants were primarily from ill and healthy humans into GF mice, in clinical studies (Table 4), the fecal microbiota of healthy volunteers were transplanted into humans with illnesses such as IBS and depression. All seven clinical studies assessed for psychiatric symptoms – six studies assessed depressive symptoms, four assessed anxiety symptoms, one assessed neuroticism, and one assessed quality of life in relation to IBS. Depression symptoms were assessed in four of the six clinical studies using the Hamilton Depression Rating Scale (HAM-D). Other scales used to assess depression symptoms were the Patient Health Questionnaire (PHQ-9), the Quick Inventory of Depressive Symptomatology (QIDS) and the Hospital Anxiety and Depression Scale, depressive sub-scale (HADS-D). All of these studies found a significant short-term improvement in depression symptoms. The long-term effects were less consistent, with three studies finding a return to baseline at week 12, week 20, and month 6 respectively (H. L. Huang et al., 2019; Mazzawi et al., 2018; Mizuno et al., 2017). Xie et al., however, found a persistent decrease in depression symptoms lasting up to 17 months after the final round of FMT (Xie et al., 2019).

Of the four studies assessing anxiety symptoms, three used the Hamilton Anxiety Rating Scale (HAM-A), and one used the Hospital Anxiety and Depression Scale, anxiety sub-scale (HADS-A). Three of the four studies found a significant improvement in anxiety symptoms following FMT (H. L. Huang et al., 2019; Kurokawa et al., 2018; Mizuno et al., 2017). Although Mizuno et al. found improvement in the anxiety scores as well, it was not significant (Mizuno et al., 2017). As with depression symptoms, Huang et al. found the anxiety scores to return to baseline within six months post-transplant and Mazzawi et al. found the improvement to be insignificant by week 20 (H.L. Huang et al., 2019, Mazzawi et al., 2018).

Neuroticism was assessed using the Eynsek Personality Questionnaire-Neuroticism (EPQ-N-12) by Mazzawi et al. A significant decrease in EPQ-N-12 scores was seen at week 3, but this returned to
baseline by week 20 (Mazzawi et al., 2018). Huang et al. assessed quality of life using the IBS-QOL scale. Scores on this questionnaire followed a similar pattern as the assessments above, with a significant improvement being observed during the first 3 months and returning to baseline by month 6 (H. L. Huang et al., 2019)

**Discussion**

The findings from reviewing the included studies suggest that FMT can affect symptoms of psychiatric disorders. This was shown for both the relief of psychiatric symptoms resulting from the transfer of microbiota from healthy donors to ill recipients and the transmission of symptoms through the transplantation of microbiota from ill donors to healthy recipients. This relationship was investigated in a variety of psychiatric disorders including depression, anxiety, anorexia and alcoholism. The transmissible properties of FMT were also well demonstrated in these studies. Notably, regardless of donor species, the transmission of psychiatric symptoms from ill donors to GF mice was consistently found. This was supported in multiple studies, with observed transference of symptoms from mouse models of depression, anxiety, chronic stress and alcoholism, and from humans with depression, to GF mice. This provides support for the concept that the gut microbiome may both contribute to the development of psychiatric disorders and be a viable target for treatment for these disorders.

All included clinical studies found improvement in the symptoms of psychiatric disorders related to these disorders following FMT from healthy donors. The beneficial aspect of FMT from healthy donors was also demonstrated preclinically where healthy transplants resulted in alleviation of depression-and anxiety-like symptoms that appeared in mice subjected to certain conditions. This alleviation of symptoms was found in mice experiencing alcohol withdrawal, as well as stressful living conditions. Though symptom alleviation was consistently observed, the duration of improvement was inconsistent. Some studies, such as Xie et al., observed an alleviation of symptoms that seemed to last indefinitely, but the majority found this to be transient (Xie et al., 2019; H. L. Huang et al., 2019; Mazzawi et al., 2018; Mizuno et al., 2017). The benefits seemed to last for only around 3–6 months, which, if used as a treatment for psychiatric disorders, is a limitation for FMT in clinical practice.

**Mechanism of Action**
The mechanism of action for how this gut microbiome modulation results in the observed symptomatic changes has yet to be fully understood. There are currently a few major hypotheses for how the microbiome affects the nervous system, resulting in symptomatic changes. The papers included in this study discussed some of these theories, with the majority postulating the mechanism to be through changes in serotonin production, immune response, and metabolism in response to microbiome changes. Serotonin transmission has long been known to be altered in depression, with selective serotonin reuptake inhibitors (SSRIs) being the most prescribed treatment for depression (Treviño et al., 2017). An estimated 90% of the body’s serotonin is produced by enterochromaffin (EC) cells in the digestive tract (Gershon, 2013). The functioning of these cells has been known to be affected by gut microbiome changes. One way that microbiome disruption is thought to affect serotonin production is through short chain fatty acids (SCFAs). SCFAs are produced by the gut microbiome through the fermentation of non-digestible carbohydrates. Some of these SCFAs are thought to be critical in the creation of serotonin by EC cells (Reigstad et al., 2015). SCFAs also play an important role in immune system functioning. The immune system can be affected by the gut simply by the fact that there are many immune cells located in the gastrointestinal tract, meaning that gut disruption can also disrupt these cells. The SCFAs produced by the gut microbiome have anti-inflammatory properties and can work to regulate the immune response (van de Wouw et al., 2018).

Many psychiatric disorders have been linked to inflammation and an increased immune response, as observed through elevated levels of immune marker cytokines (Bauer & Teixeira, 2019). It is hypothesised that this response is mediated by the NLRP3 inflammasome, a multiprotein intracellular complex that activates pro-inflammatory cytokines (Inserra et al., 2018).

Treatment Feasibility
Using FMT as a treatment for psychiatric illnesses in the future is an interesting idea that merits exploration. MDD and anxiety disorders affect millions of people worldwide and have a very large burden to the individual and society as a whole. The current gold-standard treatment for psychiatric illnesses, MDD and anxiety disorders in particular, are antidepressants medications. Though antidepressants have a relatively high efficacy, a large proportion of individuals with psychiatric
illnesses do not respond to these first-line treatments, and thus need to try alternatives (Garcia-Toro et al., 2012). Further, many antidepressant users also experience side effects such as restlessness, nausea, vomiting, anxiety, insomnia, sexual dysfunction, gastrointestinal cramps and diarrhea, and headaches that can make the arduous process of searching for effective treatments even harder (Stahl, 1998). Antidepressant medications are also still steeped in stigma further impeding one’s ability to ask for and receive help and treatment. Finally, as is stands, on average antidepressants can be costly, especially without insurance or government-funded healthcare.

There is a great need for new therapeutic targets and treatments in order to provide options and better help individuals suffering from these psychiatric illnesses. When considering the findings demonstrated in this review, FMT appears to be a promising candidate for this. The ongoing research certainly suggests its efficacy and given the few side effects and adverse events reported in these papers, may even challenge the treatments currently available. Though the treatment effect seems transient, symptoms appeared to improve relatively quickly after treatment. Another common issue seen in these indications are often to do with treatment adherence. However, given FMT effects can last up to 6 months, it may be easier to adhere to than a daily medication or a weekly psychotherapy appointment. Assuming one transplant is sufficient for therapeutic benefits lasting up to six months, the cost of treatment may be comparable to that of brand-name antidepressants, however not much is known about the costs of FMT (Eisenberg Centre at Oregon Health & Sciences University, 2007). There is potential, however, for cost of FMT to decrease, as treatment becomes more mainstream and modified.

Though the effectiveness and tolerability of FMT, as seen in these studies, makes it a promising potential treatment, there are some aspects that could limit its adoption into mainstream clinical settings. A potential drawback currently is the procedure itself. Although costs are comparable to antidepressants, it is still relatively expensive and a labor-intensive alternative to other psychiatric treatments. Additionally, the safety of FMT has also not been sufficiently understood and its associated stigma is still unknown. These points, along with the treatment still being in the early stages of research, make it difficult to fully determine the feasibility of FMT as a treatment for
psychiatric illnesses such as depression and anxiety.

Limitations
Although the studies included in this review were of good quality and contributed to a greater understanding of FMT in the context of mental health and illness, there are considerable limitations. A significant limitation in any FMT study is the fact that although research on the gut microbiome has been prolific, we still do not know what a ‘healthy microbiome’ is. Some researchers refer to a healthy microbiome as one of an individual with no overt diseases and others, however, even among those who are considered healthy, the variation in taxonomic composition is great (Lloyd-Price et al., 2016; Turnbaugh et al., 2007; Huttenhower et al., 2012).

The main limitation of the clinical studies were small sample sizes. The lack of large-scale, double blind randomized controlled trails makes it difficult to determine efficacy and safety. The majority of clinical studies also assessed the psychiatric symptoms in individuals with IBS, and not necessarily those exclusively with psychiatric disorders. This means that, though there was clear improvement if psychiatric symptoms, it cannot conclusively be said that FMT will improve the symptoms of individuals with psychiatric disorders. Additionally, it is possible that the improvement of psychiatric symptoms is secondary to the improvement of gastrointestinal symptoms associated with IBS, thus is not a direct relationship.

For the preclinical studies using human donors, the sex of the mice and donors was a major limitation, given most studies used donors or mice of only male sex. Given that there are clear sex and gender differences in the prevalence and symptomatology of mental illnesses, further research is warranted to determine if sex and gender have an effect on the efficacy of FMT procedures. Some of these studies also included donors that were taking various medications, including antidepressants, which may have affected the results. Additionally, the administration of antibiotics to create GF recipient mice and the variability in FMT administration protocol make the findings difficult to translate. For instance, some recipients received multiple FMTs, while others received only one and the justification for choosing donors varied. The heterogeneity of indications studied also creates difficulty in knowing, with any certainty, how efficacious this procedure will be for a given indication. Without a consensus
on a standard procedure for conducting this research, it is difficult to compare results between studies.

Conclusion

With high individual variability in symptomatology and prognosis, high levels of comorbidity with other disorders, genetic and environmental influences, progress in research in treatment of psychiatric disorders has been challenging. Given the huge heterogeneity of psychiatric disorders, finding treatment that works for all patients is not achievable, especially given the range of factors that influence the disorder and treatment response. While the research in this field is far from complete, the potential of targeting the gut-brain axis using FMT to alleviate symptoms of psychiatric illness is promising. Additionally, given the adaptable nature of the gut microbiome, it may be a good representation of the individual’s history and could explain differences in risk of illness, disease course, and response to treatment. If these therapies are able to alleviate symptoms of psychiatric disorders, they could be offered to some patients as personalized, alternative, and/or adjunctive treatments to combat specific symptoms that tie together specific gut bacteria strains or the gut, as a whole, to the brain.

Abbreviations

| Abbreviation | Description |
|--------------|-------------|
| GBA          | Gut-Brain Axis |
| GI           | Gastrointestinal |
| CNS          | Central Nervous System |
| ANS          | Autonomic Nervous System |
| IBS          | Irritable Bowel Syndrome |
| BDNF         | Brain-Derived Neurotrophic Factor |
| FMT          | Fecal Microbiota Transplant |
| GAD          | Generalized Anxiety Disorder |
| MDD          | Major Depressive Disorder |
| PRISMA       | Preferred Reporting Items for Systematic Reviews and Meta-Analyses |
| CUMS         | Chronic Unpredictable Mild Stress |
| NLRP3        | NOD-, LRR- and pyrin domain-containing protein 3 |
| CSC          | Chronic Subordinate Colony |
| SHC          | Non-stressful Single Housing Colony |
| FSL          | Flinders Sensitive Line Rats |
| FRL          | Flinders Resistant Line Rats |
| SNI          | Spinal Neuropathic Injury |
| GF           | Germ Free |
| HAM-D        | Hamilton Depression Rating Scale |
| PHQ-9        | Patient Health Questionnaire-9 |
| QIDS         | Quick Inventory of Depressive Symptomatology |
| HADS(-A/D)   | Hospital Anxiety and Depression Scale (-Anxiety/Depression Specific) |
| HAM-A        | Hamilton Anxiety Rating Scale |
| EPQ-N-12     | Eynsek Personality Questionnaire-Neuroticism |
| IBS-QOL      | Irritable Bowel Syndrome - Quality of Life |
| SSRI         | Selective Serotonin Reuptake Inhibitors |
| EC           | Enterochromaffin Cells |
| SCFA         | Short-chain Fatty Acids |

Declarations
Ethics approval: Given the data is collected from publicly available information, research ethics board review is not required for systematic reviews.

Informed consent: Given there was no interaction with the participants in this study there was no informed consent required.

Availability of Data and Materials: All data analysed for and presented in this paper are from the twenty-one studies we reviewed. The data is accessible via referenced articles.

Competing Interests: RM has received consulting and speaking honoraria from Allergan, Janssen, KYE, Lundbeck, Otsuka, Pfizer and Sunovion, and research grants from CAN-BIND, CIHR, Janssen, Lallemand Health Solutions, Lundbeck, Nubiyota, OBI, OMHF and Pfizer. CW has received study funding from Lallemand Health Solutions.

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**Appendix - Search Strategy**

1. Depression OR Mood OR Stress, Psychological OR Anxiety OR Mania OR Panic OR Phobia OR Psychiatric illness

2. Microbiota Transplant OR Stool transplant OR Bacteriotherapy OR Microbial Ecosystem Therapy OR Microbial/Microbe Therapy

3. 1 AND 2

   a. MEDLINE: 206 Results
   b. OVID PsycINFO: 15 Results
   c. EMBASE, 206 Results
   d. Web of Science, 111 Results
   e. CINAHL: 1 Result

**Figures**
Figure 1

Flow chart showing literature search and screening process using PRISMA process.

Supplementary Files

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