The Safety, Efficacy, and Tolerability of Microbial Ecosystem Therapeutic-2 in People With Major Depressive Disorder and/or Generalized Anxiety Disorder: A Phase 1, Open-Label Study

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Research Article

Keywords: gut-brain axis, microbiome, microbial ecosystem therapeutic, depression, anxiety

Posted Date: April 8th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-374466/v1

Abstract

Background: Recent studies have investigated the potential of treatments that modify the gut microbiome, such as fecal microbiota transplantation (FMT) and probiotics, in individuals with psychiatric illnesses. The aim of this study was to investigate the safety, tolerability, and efficacy of a novel gut microbiome therapeutic, Microbial Ecosystem Therapuetic-2 (MET-2), in people with depression and anxiety.

Methods: In this phase 1, open-label trial, twelve adults diagnosed with Major Depressive Disorder and/or Generalized Anxiety Disorder were recruited. Participants consumed orally once daily an encapsulated microbial therapeutic, containing 40 strains of bacteria purified and lab-grown from a single healthy donor stool, for 8 weeks. Participants were assessed biweekly using clinical scales and questionnaires in order to evaluate the safety, efficacy, and tolerability of the therapeutic.

Results: The therapeutic was found to be generally safe and tolerable, with limited adverse events and side effects, and no serious adverse events. Of the twelve individuals included in this study, nine responded to treatment (50% improvement in MADRS and/or GAD-7 scores from baseline to week 8 visit). Over the course of 10 weeks MET-2 significantly decreased mean MADRS and GAD-7 scores, MADRS [$F(5, 55) = 8.784$, $p<0.0001$ and GAD-7 $F(5,55) = 9.638$, $p<0.0001$].

Conclusion: The findings of this study are the first to provide evidence for the role of microbial ecosystem therapy in treating depression and anxiety. However, a double-blind, randomized controlled trial with a larger sample size is needed for more conclusive results.

Trial Registration: This study was registered with clinicaltrials.gov (NCT04052451) on 09/08/2019.

1. Background

Major Depressive Disorder (MDD) is highly prevalent, affecting over 264 million people of all ages, globally (1) and associated with high societal and personal burden. MDD is characterized by persistent depressed mood and/or loss of interest or pleasure and symptoms that cause clinically significant distress or impairment (2). MDD is often comorbid with other mental and physical illnesses, such as Generalized Anxiety Disorder (GAD) (3). GAD is characterized by excessive anxiety and worry about life circumstances, such as work, school, relationships, etc. (4) and has a lifetime prevalence of 5% (5), (3).The psychological symptoms of these illnesses are often accompanied by physical symptoms, such as abdominal issues, pain, and poor sleep quality (6), (7). Though there are a variety of gold standard and novel treatment methods that target symptoms of depression and anxiety (8), the heterogeneity of these disorders has led to difficulty in research in the field of mood and anxiety disorders (9).

Recent research has been exploring the connections between mood and anxiety disorders and the gut microbiome. As such, the “gut-brain axis” (GBA) which consists of bidirectional signaling between the gastrointestinal (GI) tract and the brain (10), has become a novel target for treatment of mood and

anxiety symptoms. Studies suggest that this improvement of depressive and anxiety symptoms and severity may be related to the recolonization of the gastrointestinal tract with healthy bacteria (11).

The purpose of this study was to evaluate the safety, efficacy, and tolerability of a GBA treatment method known as Microbial Ecosystem Therapeutic-2 (MET-2). MET-2 comes in encapsulated form and is composed of forty purified strains of lyophilized bacteria from a healthy 25-year-old donor and is chosen for its favorable safety profile. MET-2 was developed in response to the growing body of literature supporting the ameliorative effects of fecal microbiota transplantation (FMT) on symptoms of depression. FMT is a procedure used to recolonize a patient's gut microbiota through the transplantation of feces from a donor to the recipient. A recent systematic review details the current literature surrounding the safety, efficacy and mechanisms of action for FMT (11). Though FMT has been found to be effective in many cases, it is still an arduous, expensive and invasive procedure. MET-2 provides an exciting alternative to FMT, with the possibility of conferring the same ameliorative properties with an easier and more tolerable mode of delivery. The objectives of this study were to assess the safety, tolerability, efficacy of MET-2.

2. Methods

2.1 Study Design

This study was a 10-week, open-label, phase 1 clinical trial conducted out of Providence Care Hospital in Kingston, Ontario, Canada. This study was approved by the Health Science Regulatory Ethics Board of Queen's University, Ontario, Canada. The protocol has been previously published here: https://www.researchprotocols.org/2020/6/e17223/ (11). This study was registered with clinicaltrials.gov (NCT04052451, 09/08/2019).

2.2 Participants

Inclusion criteria for participants were an age of 18 to 65, a diagnosis of Major Depressive and/or Generalized Anxiety Disorder using the Mini International Neuropsychiatric Interview (MINI), and no current use of any antidepressant medications. Mood, anxiety, sleep, GI symptoms and severity of illness was assessed at screening using the Montgomery-Asberg Depression Rating Scale (MADRS), GAD 7-item scale (GAD-7), and other clinical scales. A minimum score of 15 on the MADRS or 8 on the GAD-7 were also required for inclusion in the study. For full set of inclusion, exclusion, and discontinuation criteria and detailed study design, see previously published protocol (12). Participants were recruited from the local community using posters and online advertisements. Signed written informed consent was obtained from all participants.

2.3 Intervention

The investigational product in this study was MET-2 – capsules composed of forty purified strains of lyophilized bacteria from a healthy 25-year-old donor. MET-2 was developed by NuBiyota in Guelph, ON, Canada. During the 8 weeks of treatment, all participants consumed orally, three MET-2 capsules/day at

0.5g of MET-2 per capsule, each containing 3.2 x 10^5-3.2x10^{11} colony-forming units (CFUs). This was known as the maintenance dose. Additionally, a loading dose of 5g of MET-2 was taken for two days immediately following baseline and week 2 visits for all participants and following week 4 visit for non-responders (lacking reduction in MADRS or GAD-7 scores by 50% by this time point) (12). Mood, anxiety, GI symptoms and sleep quality were assessed at all biweekly treatment visits. At the week 10 follow-up, only mood and anxiety were assessed.

2.4 Outcome Measures

The clinical measures included: the GAD-7 (13) to assess anxiety symptoms and severity, the MADRS (14) to assess depressive symptoms and severity, the Snaith-Hamilton Pleasure Scale (SHAPS) (15) to assess anhedonia, the quick inventory of depressive symptomatology (QIDS) (16) to assess depressive symptoms, the gastrointestinal symptom rating Scale (GSRS) (17) to assess GI symptoms, the Pittsburgh sleep quality index (PSQI) (18) to assess subjective sleep quality, and the clinical global impressions scale (CGI-S) (19) to assess illness severity.

Participants used a personal mood and symptom log to track any new symptoms that they have been experiencing since the beginning of treatment (20), assess the tolerability of treatment, and keep track of their mood and sleep. Adverse events (AEs) were assessed and recorded at all visits; they were categorized by frequency, severity, and causality. Only adverse events rated as a grade 2 or above were included in the analysis. Investigational product safety was assessed via recorded symptoms on the Toronto Side Effects Scale (TSES) (21–23), the personal logs, and AEs (12).

2.5 Statistical Analysis

GraphPad Prism 8 was used to analyze all data from clinical measures obtained throughout the study and to create plots. A repeated-measures analysis of variance (ANOVA) was used to analyze changes in clinical measures from baseline to week 10. Paired T-tests were used to compare clinical measure means at each time point to baseline. If a participant returned after first course of treatment and later withdrew, their final clinical scores and were projected to Week 10. This study was registered with clinicaltrials.gov (NCT04052451, 09/08/2019).

2.6 Role of the funding source

The funder, Nubiyota, provided the investigational product and though they had a role in other data analysis in the trial, that data is not reported in this paper. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

3. Results

3.1 Study population

The study cohort consisted of twelve participants, eight of which were female, with a total mean age of 28.8 ± 12.8 years. The participants were recruited from May 16, 2019 to November 7, 2019. The trial

profile can be found in Fig. 1. The study population was fairly diverse, with ages ranging from 19 to 59 years of age, and representation from four different ethnicities. Further demographic information can be found in Table 1. Ten of the twelve participants were diagnoses with both MDD and GAD, six of which were currently experiencing a Major Depressive Episode (MDE) with the remainder having experienced at least one MDE in the past. The two remaining participants had sole diagnoses of MDD and GAD respectively. All participants were combined into one group for analysis due to the high comorbidity of the two psychiatric illnesses. Baseline MADRS and GAD-7 scores were 19.0 ± 4.8 and 13.6± 4.0 respectively.

Table 1
Demographics

	Characteristic	N	%
Gender	Male	4	33.3
	Female	8	66.7
Diagnosis	MDD only	1	8.3
	GAD only	1	8.3
	MDD and GAD	10	83.3
Ethnicity	Caucasian	8	66.7
	Chinese	2	16.7
	Latin American	1	8.3
	South Asian	1	8.3
Education Level	High School Graduate/Some College	3	25
	College/University Degree	9	75
Employment Status	Student	7	58.3
	Working	2	16.7
	On Leave/Disability	3	25

3.2 Efficacy Measures

The principal efficacy measures used were the MADRS, GAD-7 and CGI-S. A one-way repeated measured analysis of variance (ANOVA) showed significant reductions in mean MADRS [$F(5, 55) = 8.784$, $p < 0.0001$] scores between visits. Multiple comparisons with Bonferroni adjustments showed a significant reduction from baseline MADRS scores (19.0 ± 4.8) to week 6 (11.3 ± 8.0, $p = 0.0028$), week 8 (8.7 ± 8.7, $p < 0.0001$), and week 10 (8.3 ± 9.3, $p < 0.0001$). There was a slight reduction from baseline MADRS scores to week 2 (14.67 ± 6.9) and week 4 (14.7 ± 6.9), however, neither were significant ($p = 0.4361$, $p = 0.0831$, respectively). Additionally, eight of twelve participants were responders and improved by at least 50% in MADRS scores by week 8, of which seven remained responders by week 10. Of those that remained

responders (n = 7), one still worsened in mood symptoms, but not below 50% from baseline. Similarly, results from the one-way repeated measured ANOVA showed a significant reduction in mean GAD-7 scores [$F(5,55) = 9.638$, $p < 0.0001$]. Multiple comparisons showed a significant reduction from baseline GAD- 7 scores (13.58 ± 4.0) to week 4 (9.2 ± 5.1, $p = 0.0038$), week 6 (7.7 ± 4.5, $p < 0.0001$), week 8 (7.3 ± 6.6, $p < 0.0001$), and week 10 (7.5 ± 6.5, $p < 0.0001$). There was a slight reduction from baseline GAD-7 scores to week 2 (10.9 ± 4.5), which was not significant ($p = 0.3268$). Additionally, seven of twelve participants were responders and 6 improved by at least 50% in GAD-7 scores by week 8, of which five remained responders by week 10. Of those that remained responders (n = 5), one still worsened in anxiety symptoms, but not below 50% from baseline. A significant reduction in mean CGI-S scores was seen [$F(4, 44) = 8.709$, $p < 0.0001$], from baseline (3.67 ± 0.78) to week 6 (2.67 ± 0.98, $p = 0.0028$) and week 8 (2.33 ± 1.07, $p < 0.0001$). Although a slight reduction was seen from baseline CGI-S scores to week 2 (3.25 ± 0.75) and week 4 (3.25 ± 0.97), neither were significant ($p > 0.999$).

Additional efficacy measures included the QIDS-SR16, SHAPS, and PSQI, three self-report measures evaluating depressive symptomology, anhedonia, and subjective sleep quality respectively. QIDS-SR16 scores were found to be significantly reduced [$F(2.40, 26.42) = 7.111$, $p = 0.002$], between baseline (12.42 ± 3.14) to week 6 (7.33 ± 5.83, $p = 0.0195$) and week 8 (6.75 ± 6.17, $p = 0.013$). Reductions from baseline to week 2 (11.17 ± 4.88) and week 4 (8.67 ± 6.31) were not significant ($p = 0.913$ and 0.329, respectively). No significant reduction in mean SHAPS scores was found [$F(2.16, 23.82) = 0.958$, $p = 0.404$], between baseline (3.92 ± 3.99) to week 2 (3.33 ± 3.65), week 4 (2.92 ± 4.64), week 6 (3.42 ± 4.36), or week 8 (2.58 ± 3.92). Results from tests of between-subject contrasts in a one-way repeated measures ANOVA showed a significant reduction in mean PSQI scores [$F(4, 44) = 3.100$ $p = 0.025$]. However, multiple comparisons between baseline PSQI (9.33 ± 2.83) and week 2 (8.50 ± 3.00), week 4 (7.08 ± 3 .98), week 6 (7.92 ± 3.45), and week 8 (7.00 ± 3.83) were all not significant. Graphs showing the change in efficacy outcome measures over the course of the study can be found in Fig. 2.

3.3 Safety and Tolerability Measures

A total of eleven adverse events and zero serious adverse events were reported by participants during the course of the study. The majority of these adverse events were declared unrelated to the investigational product by participants' family physicians and/or the principal investigator. The most common adverse event was a stomach-ache, but this was reported multiple times by one the same participant. Only one reported adverse event was considered to have a possible relationship to the study product – an instance of a stomach-ache rated level 2 with moderate pain. The full list of reported adverse events can be found in Table 2. As MET-2 is a therapeutic targeting the gut, its effect on gastrointestinal symptoms was measured with the GSRS at five time points during the course of the study. One-way repeated measures ANOVA showed no significant change in mean GSRS scores [$F(2.08, 22.90) = 0.868$, $p = 0.4371$], between baseline (27.58 ± 15.38) to week 2 (25.33 ± 7.99), week 4 (23.50 ± 8.20), week 6 (23.33 ± 10.10), or week 8 (23.42 ± 9.54). A graph depicting the change in GSRS scores over the course of the study can be found in Fig. 3. Side effect frequency and severity was measured using the TSES. 31 side effects with an intensity greater than 14 were reported. These side effects can be found in Table 3.

Table 2
Adverse Events

Adverse Events	Number of Incidences
Stomachache	3
Rash/Black Dots	1
Eye Pain	1
Bloating	2
Diarrhea	1
Lower Abdomen Cramps	1
Itchy Throat	1
Vomiting	1
Anxiety Attack	1
Panicky Feeling Jitters	1
Heart Palpitations	2
Nightmares	1
Abdominal Pain	1

Table 3
TSES side effects with an intensity greater than 14

Side Effect	Number of Incidences
Nervousness	5
Agitation	3
Tremor	2
Dyspepsia	1
Nausea	1
Diarrhea	1
Weakness/Fatigue	3
Drowsiness	2
Increased Sleep	1
Decreased Sleep	1
Flushing	3
Headache	1
Dry Mouth	1
Anorgasmia	1
Decreased Libido	1
Delayed Ejaculation	1
Impotence	1
Bloating	1
Heart Palpitations	1

4. Discussion

In this study, the novel gut microbiota targeting treatment for symptoms of Major Depressive Disorder and Generalized Anxiety Disorder, MET-2, was found to be safe, generally tolerable, and efficacious. These findings are in line with what was expected as current literature regarding fecal microbiota transplantation and suggest that gut microbiome augmentation can result in the alleviation of symptoms in a variety of psychiatric illnesses including MDD and GAD. Pre-clinical research has found both the conferment of psychiatric symptoms through the transplantation of fecal microbiota from animals displaying behaviours related to psychiatric illnesses to antibiotic-treated animals (24–27),as well as the

amelioration of psychiatric symptoms after FMT from healthy animals to those displaying psychiatric symptoms (28, 29). Clinical research has found the transplantation of microbiota from a healthy donor to an ill recipient often results in the alleviation of psychiatric symptoms (11). As MET-2 is a collection of bacteria cultured from the gut of a healthy human donor, it was suspected, and subsequently supported by this study, that treatment with MET-2 would result in symptom improvement similar to that seen in clinical FMT studies.

When comparing studies, MET-2 was found to be as safe as FMT since both the FMT studies and this study reported relatively few adverse events that were deemed to be related to the treatment. When comparing the tolerability and burden to the patient, it is expected that MET-2 would be less of a burden as FMT can be a rather arduous process, but further research would be needed to determine which treatment is more feasible.

5. Limitations

This study addresses some of the limitations in the literature such as the safety and stigma associated with treatments like fecal transplants, labor costs, and evaluates the use of a GBA treatments without other treatment interference, to name a few. The main limitation of this study, as with the reviewed clinical studies, was the small sample size and open label design. The lack of large-scale, double-blind randomized controlled trials makes it difficult to determine efficacy and safety. The small sample size, in addition to the missing data, prevents large-scale analyses between parameters and may be the reason for limited significance in data, given the trends that were seen. Additionally, the lack of a placebo arm, in conjunction with the limited power in sample size, suggests the results may be merely due to placebo effect or chance. That said, typically the placebo effect is around 30–40% in psychiatric indications, and our study response was 75%, suggesting it is unlikely to be a placebo effect. It also seems that the effects of MET-2 may begin to wear off after stopping treatment, however, given our study was only 10 weeks, and the follow up period was only 2 weeks, we cannot be certain at what point and rate the effects diminish. The follow-up period in future studies will need to be longer to determine if there is a need for maintenance therapy.

Further, given the nature of the study, participants were asked to come in every two weeks for an in-person visit, where inevitably they have an opportunity to open up about their mood and related symptoms – which can be therapeutic in and of itself. This could have contributed to the quick improvement in mood and anxiety symptoms.

Finally, though we look to see if participants may have a diagnosis for an eating disorder or alcohol dependence, we do not ask how often these individuals are drinking or what their eating habits are. These components may have an effect on response to or transiency of treatment.

6. Conclusion

In summary, our study has found MET-2 to be efficacious as it significantly improves mood and anxiety symptoms in as early as four and two weeks of treatment, respectively. We found nine out of twelve participants to have improved by at least 50% in their MADRS or GAD-7 scores from start to end of treatment. This improvement was seen in conjunction with limited side effects and lack of serious adverse events.

With high individual variability in symptomatology and prognosis, high concentrations of comorbidity with other disorders, and genetic and environmental influences, progress in research in treatment of psychiatric disorders has been challenging. 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.

With the complicated heterogeneity of psychiatric disorders, finding one treatment that works for all patients is not achievable, especially given the range of factors that influence the disorder and treatment response. Our study has shown, MET-2 to considerably improve mood and anxiety symptoms, with limited side effects. While the research in this field is far from complete, the potential of targeting the gut-brain axis using GBA treatments, such as FMT and MET-2 to alleviate symptoms of psychiatric illness is promising. That said, further large-scale research in exclusively psychiatric indications is needed to prove gut repopulation treatments, specifically MET-2, can be effective treatment methods.

List Of Abbreviations

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

Authors' Contributions: ACM is the corresponding author and was involved in designing and conducting the clinical trial, collecting and analysing data, and writing, editing, and submitting this manuscript. EF was involved in writing and editing this manuscript. RM was the principle investigator of the study and was involved in writing and editing of the manuscript.

Consent for publication: Not applicable

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.

Ethics approval and consent to participate: This study was approved by the Health Science Regulatory Ethics Board of Queen's University, Ontario, Canada, and all methods were performed in accordance to the Declaration of Helsinki. Signed written informed consent was obtained from all participants in this study for the collection of all forms of data.

Funding: The current study was sponsored by and the investigational product provided by NuBiyota LLC.

Acknowledgements: This study was funded by NuBioyta LLC.

Availability of Data and Materials: The datasets generated and/or analysed during the current study are not publicly available as of yet but are available from the corresponding author on reasonable request.

References

1. James SL, Abate D, Abate KH, Abay SM, Abbafati C, Abbasi N, et al. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. The Lancet. 2018 Nov 10;392(10159):1789–858.
2. American Psychiatric Association. Depressive Disorders. In: Desk Reference to the Diagnostic Criteria From DSM-5. 5th ed. Arlington, VA: American Psychiatric Association; 2013. p. 94–7.
3. Kessler RC, Chiu WT, Demler O, Walters EE. Prevalence, Severity, and Comorbidity of Twelve-month DSM-IV Disorders in the National Comorbidity Survey Replication (NCS-R). Arch Gen Psychiatry. 2005 Jun;62(6):617–27.
4. Parekh R. What Are Anxiety Disorders? [Internet]. 2017 [cited 2020 Sep 22]. Available from: https://www.psychiatry.org/patients-families/anxiety-disorders/what-are-anxiety-disorders
5. Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. Arch Gen Psychiatry. 2005 Jun;62(6):593–602.

6. Otheman Y, Fakir A, Kadiri M, Bichra MZ. [Frequency of physical symptoms in anxiety-depressive disorders: cross-sectional study in a population of 202 psychiatric consultants]. Pan Afr Med J. 2018;31:149.
7. Johnson EO, Roth T, Breslau N. The association of insomnia with anxiety disorders and depression: exploration of the direction of risk. J Psychiatr Res. 2006 Dec;40(8):700–8.
8. Kennedy SH, Lam RW, McIntyre RS, Tourjman SV, Bhat V, Blier P, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 Clinical Guidelines for the Management of Adults with Major Depressive Disorder: Sect. 3. Pharmacological Treatments. Can J Psychiatry. 2016;61(9):540–60.
9. Goldberg D. The heterogeneity of "major depression." World Psychiatry. 2011;10(3):226–8.
10. Carabotti M, Scirocco A, Maselli MA, Severi C. The gut-brain axis: interactions between enteric microbiota, central and enteric nervous systems. Ann Gastroenterol. 2015;28(2):203–9.
11. Chinna Meyyappan A, Forth E, Wallace CJK, Milev R. Effect of fecal microbiota transplant on symptoms of psychiatric disorders: a systematic review. BMC Psychiatry. 2020 Jun 15;20(1):299.
12. Meyyappan AC, Milev R. The Safety, Efficacy, and Tolerability of Microbial Ecosystem Therapeutic-2 in People With Major Depression and/or Generalized Anxiety Disorder: Protocol for a Phase 1, Open-Label Study. JMIR Research Protocols. 2020;9(6):e17223.
13. Spitzer RL, Kroenke K, Williams JBW, Löwe B. A brief measure for assessing generalized anxiety disorder: the GAD-7. Arch Intern Med. 2006 May 22;166(10):1092–7.
14. Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. Br J Psychiatry. 1979 Apr;134:382–9.
15. Snaith RP, Hamilton M, Morley S, Humayan A, Hargreaves D, Trigwell P. A scale for the assessment of hedonic tone the Snaith-Hamilton Pleasure Scale. Br J Psychiatry. 1995 Jul;167(1):99–103.
16. Rush AJ, Trivedi MH, Ibrahim HM, Carmody TJ, Arnow B, Klein DN, et al. The 16-Item Quick Inventory of Depressive Symptomatology (QIDS), clinician rating (QIDS-C), and self-report (QIDS-SR): a psychometric evaluation in patients with chronic major depression. Biol Psychiatry. 2003 Sep 1;54(5):573–83.
17. Svedlund J, Sjödin I, Dotevall G. GSRS–a clinical rating scale for gastrointestinal symptoms in patients with irritable bowel syndrome and peptic ulcer disease. Dig Dis Sci. 1988 Feb;33(2):129–34.
18. Buysse DJ, Reynolds CF, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Res. 1989 May;28(2):193–213.
19. Guy W. ECDEU assessment manual for psychopharmacology. Rev. 1976. Rockville, Md: U.S. Dept. of Health, Education, and Welfare, Public Health Service, Alcohol, Drug Abuse, and Mental Health Administration, National Institute of Mental Health, Psychopharmacology Research Branch, Division of Extramural Research Programs; 1976. 603 p.
20. Black Dog Institute. Black Dog Institute - Mental Health Research for the Whole Community [Internet]. Black Dog Institute. [cited 2020 Sep 28]. Available from: https://www.blackdoginstitute.org.au/

21. Vanderkooy J, Kennedy S, Bagby R. Antidepressant side effects in depression patients treated in a naturalistic setting: a study of bupropion, moclobemide, paroxetine, sertraline, and venlafaxine [Internet]. Vol. 47, Canadian journal of psychiatry. Revue canadienne de psychiatrie. Can J Psychiatry; 2002 [cited 2020 Sep 29]. Available from: http://pubmed.ncbi.nlm.nih.gov/11926080/
22. Yin OQ, Wing Y-K, Cheung Y, Wang Z-J, Lam S-L, Chiu HF, et al. Phenotype-genotype Relationship and Clinical Effects of Citalopram in Chinese Patients. Journal of Clinical Psychopharmacology. 2006 Aug;26(4):367–372.
23. Crawford AA, Lewis S, Nutt D, Peters TJ, Cowen P, O'Donovan MC, et al. Adverse effects from antidepressant treatment: randomised controlled trial of 601 depressed individuals. Psychopharmacology (Berl). 2014;231(15):2921–31.
24. Li N, Wang Q, Wang Y, Sun A, Lin Y, Jin Y, et al. Fecal microbiota transplantation from chronic unpredictable mild stress mice donors affects anxiety-like and depression-like behavior in recipient mice via the gut microbiota-inflammation-brain axis. Stress. 2019 Sep 3;22(5):592–602.
25. Lv W, Wu X, Chen W, Li Y, Zhang G, Chao L, et al. The Gut Microbiome Modulates the Changes in Liver Metabolism and in Inflammatory Processes in the Brain of Chronic Unpredictable Mild Stress Rats. Oxidative Medicine and Cellular Longevity. 2019 Oct 24;2019:1–14.
26. Xiao H, Ge C, Feng G, Li Y, Luo D, Dong J, et al. Gut microbiota modulates alcohol withdrawal-induced anxiety in mice. Toxicology Letters. 2018 May;287:23–30.
27. Yang C, Fang X, Zhan G, Huang N, Li S, Bi J, et al. Key role of gut microbiota in anhedonia-like phenotype in rodents with neuropathic pain. Transl Psychiatry. 2019 Dec;9(1):57.
28. Langgartner D, Vaihinger CA, Haffner-Luntzer M, Kunze JF, Weiss A-LJ, Foertsch S, et al. The Role of the Intestinal Microbiome in Chronic Psychosocial Stress-Induced Pathologies in Male Mice. Front Behav Neurosci. 2018 Oct 26;12:252.
29. Tillmann S, Abildgaard A, Winther G, Wegener G. Altered fecal microbiota composition in the Flinders sensitive line rat model of depression. Psychopharmacology. 2019 May;236(5):1445–57.

Figures

Figure 1

Trial profile * Study population consists of anyone that attended more than one post-baseline (first treatment) visit

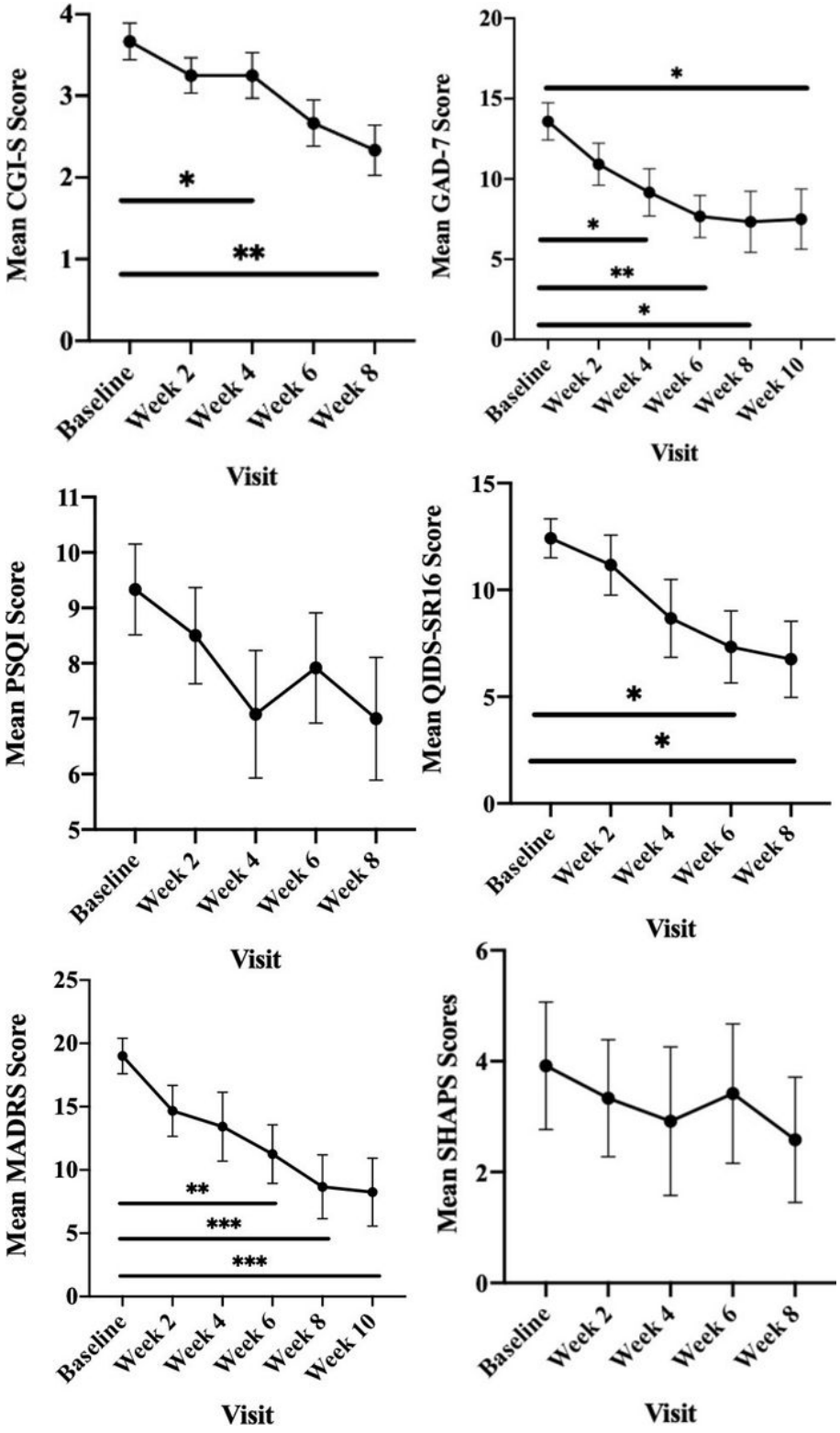

Figure 2

Graphs of Efficacy Measures Top Left Panel: 2(A) Change in mean CGI-S score Middle Left Panel: 2(B) Change in mean PSQI score Bottom Left Panel:2(C) Change in mean MADRS score Top Right Panel: 2(D) Change in mean GAD-7 score Middle Right Panel: 2(E) Change in mean QIDS-SR16 score Bottom Right Panel: 2(F) Change in mean SHAPS score

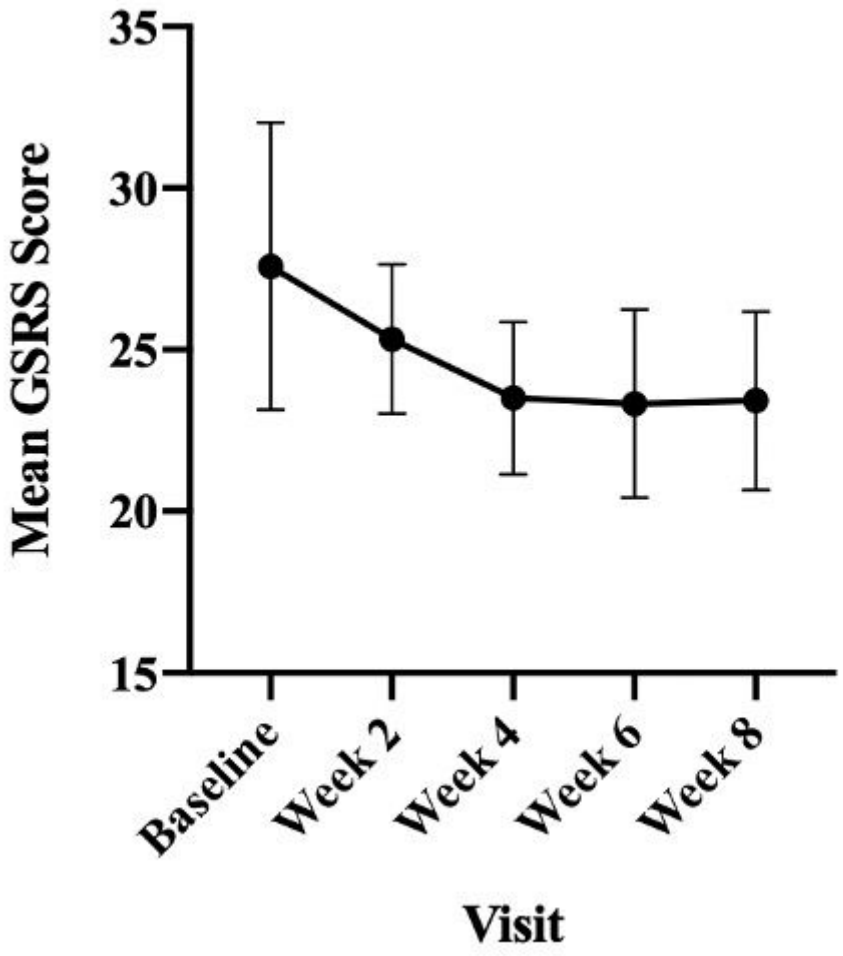

Figure 3

Mean gastrointestinal symptom scores over time