DOI: 10.1111/bdi.13187

CLINICAL CARE

BIPOLAR DISORDERS WILEY

Faecal microbiota transplantation for bipolar disorder: A detailed case study

Gordon Parker | Michael J. Spoelma | Nicholas Rhodes

Discipline of Psychiatry and Mental Health, School of Clinical Medicine, University of New South Wales, Sydney, Australia

Correspondence
Professor Gordon Parker, Discipline of Psychiatry and Mental Health, Level 1, AGSM Building, Gate 11, Botany Street, UNSW Sydney NSW 2052, Australia.
Email: g.parker@unsw.edu.au

Funding information
National Health and Medical Research Council, Grant/Award Number: 1176689

1 | INTRODUCTION

As observed by Green et al.,[1] faecal microbiota transplantation (FMT) has a lengthy history dating back to the fourth century AD in China, where it was used to treat conditions such as diarrhoea and food poisoning. Its contemporary salience reflects awareness that the gastrointestinal tract is an ecosystem of bacteria and other microorganisms (i.e., the gut microbiome) which, either by themselves or when 'disrupted' (by an antibiotic for example), may result in a range of conditions or symptoms. FMT is designed to restore healthy microorganisms via donor stools. Its most clearly established application is in the management of clostridium difficile infection, but there are numerous case reports arguing for its benefits across a range of gastrointestinal conditions (e.g., ulcerative colitis, Crohn's disease) as well as myriad disparate disorders (e.g., multiple sclerosis, Parkinson's disease) and medical states (e.g., obesity).

In separate papers, Green et al.[1,2] considered its potential relevance to the management of mood disorders, and the steps in their arguments are now summarised. First, changing the gut microbiota in animals can modulate "depression-like" behaviours. Second, there have been several studies reporting differences in human gut microbiota between those with depression and controls. Third, gut microbiota may modify a number of systems and physiological processes implicated in depression, including inflammation and immune activation, oxidative stress, the hypothalamic-pituitary-adrenal axis, cortisol levels, and neurotransmitter/neuropeptide regulation. In relation to bipolar disorder, Cooke et al.[3] referenced four papers detailing specific alterations in gut microbiome composition in bipolar patients which correlated with "illness severity," while Xu et al.[4] overviewed studies showing differing gut microbiota and probiotics improving cognition and executive functioning in bipolar patients.

So far, no trials have been published evaluating FMT for those with depressive or bipolar conditions, but one Canadian placebo-controlled trial for bipolar depression[3] is nearing completion.[2] The only currently published data is one (very brief) case report published by Hinton.[5] The patient was a woman in her late twenties who had been diagnosed with bipolar I disorder. Pre-FMT she received multiple psychotropic drugs (including the mood stabilisers lithium, sodium valproate, and lamotrigine) but reported that they were ineffective and generated multiple side effects such as weight gain. She had nine FMT treatments over eleven months and, within six months, reported being symptom-free while her medications (lithium, lamotrigine, quetiapine) were able to be ceased. Hinton recorded that, on review months later, she had remained symptom-free, was taking no medication, had lost 33 kg, was working, and was no longer "functionally disabled".

The first author of this paper had a patient inquire as to whether he had any views against the patient trialling FMT. No objection was raised, and close self-monitoring of the patient's progress allowed for rich information to be collected. This case study describes this patient's experiences with FMT, with the aim of further advancing understanding of procedural nuances as well as its potential salience and therapeutic benefit for patients with bipolar disorder and who have not responded to orthodox management strategies.

2 | METHODS

The subject of this study is a 28-year-old (as of 2022) male with bipolar II disorder from Sydney, Australia. At initial assessment by the first author in 2014, the subject first detailed severe anxiety present from the age of 10, meeting the criteria for generalised anxiety and panic disorder. The panic attacks impaired his capacity to leave his house in his late teens. He also described checking behaviours, but they were not severe enough to warrant a diagnosis of obsessive-compulsive disorder. Longstanding issues of problems with concentration, being distracted, and being somewhat hyperactive raised the possibility of a mild attention deficit hyperactivity disorder (ADHD).

At the age of 10, he also developed depressive episodes. Symptoms for recent episodes leading to his initial assessment included a severely depressed mood, suicidal thoughts, anergia, impaired concentration ("brain fog"), psychomotor retardation, and insomnia. Such symptoms were commonly accompanied by irritability and anxiety spikes. At the age of 15 he developed his first hypomanic episode, waking up "*feeling like everything was just amazing. Even my skin was tingling*." Episodes would last days to weeks, with features including increased energy ("*feeling on fire and that nothing can stop me*"), excessive talk and being loud, spending excessively, feeling he "*could do anything*" ("*there were "no no's"*), needing less sleep (2–3 hours per night), not feeling tired, and feeling bulletproof. Euthymic periods were brief, generally lasting only a few days. There was a family history of depression in one first-degree relative, and probably bipolar disorder in a second-degree relative. From the age of 15 the mood swings had become more intense over time, while respite periods became progressively briefer and then virtually non-existent.

In the absence of any psychotic experiences, a bipolar II diagnosis was made. Lamotrigine was initiated and titrated over eight weeks to 200 mg nocte with considerable improvement in depression and hypomanic states over the next six months, while his anxiety symptoms became less distinctive. Late in the following year, mood swing episodes became more distinctive again, and the lamotrigine was progressively increased to 400 mg/day while low-dose quetiapine (25 mg) was prescribed to assist a severe and protracted period of insomnia. Again, symptom improvement was reported. Over the next year, he increased his quetiapine dosage progressively to 250 mg/day (most commonly) to assist with insomnia, finding that it would allow him to have 8–10 hours of sleep. He took it for the next five years, judging that its benefits outweighed a number of side effects (i.e., dependence, feeling clouded the following mornings for several hours, developing severe food cravings and having distinct weight gain). During that period, he had moderate mood stability (albeit broken by some severe hypomanic and depressive episodes) but completed a university course and had part-time employment.

In 2020, he developed a febrile illness, with investigations at that time identifying a Type 1 Brugada ECG pattern. The reviewing cardiologist noted that his lamotrigine medication was therefore contraindicated and he was switched to sodium valproate (progressively increased briefly to 800 mg/day) in conjunction with quetiapine, but after developing a number of side effects (e.g., irritability, rapid and at times incoherent speech, sleep deprivation) he elected to lower the sodium valproate to 200 mg till ceasing it the day after FMT. That regime controlled his mood to only some degree, and the hypomanic episodes during this time were distinctive. He did observe some worsening in his ADHD symptoms that year.

In July 2019, on his own initiative, he had commenced taking the following probiotics: lactobacillus acidophilus (32 billion CFU), lactobacillus rhamnosus (4 billion CFU), and saccharomyces cerevisiae (boulardii; 4 billion CFU). He observed: "*Overnight, I noticed a huge relief of symptoms. My mind was much more relaxed and not as heavy with mental noise or traffic. I had greater control over food cravings, especially at night. I was able to figure out what was causing the intense depressive episodes, which seemed to be sugar or sugary foods. I tested this hypothesis one night by consuming a big teaspoon of Nutella* [a sweetened hazelnut cocoa spread whose principal ingredients are sugar and palm oil]. *Within minutes, a depressive episode kicked in and I was stuck on the couch catatonic for about five hours. The probiotic assisted with cravings so much that I eventually lost weight to the point where I was lighter than I was prior to my bipolar diagnosis. The probiotics prevented episodes of mania that would occur if I stopped taking my mood stabilisers. I found that, if I only took saccharomyces cerevisiae (boulardii), it would induce distinctive irritability and hypomania, and that, if I didn't take saccharomyces cerevisiae while taking other probiotics, depressive episodes would occur.*" Such changes encouraged him to read widely on microbiome research. After reading the case report by Green et al.,[1] and noting the relative lack of benefit from sodium valproate, he elected to trial FMT.

The FMT procedure was undertaken by a specialist gastroenterologist in September 2020. Multiple pre-screening stool, urine and

KEY MESSAGE

Faecal microbiota transplantation (FMT) has been proposed as a beneficial treatment for multiple conditions, including mood disorders. This case report (the second in the literature) provides detailed longitudinal information of successful FMT treatment for a patient with bipolar disorder. FMT may be a management option for treatment-resistant bipolar disorder.

LEARNING POINTS

- Faecal microbiota transplants may show promise as a therapy for those with a treatment-resistant bipolar disorder.
- Symptom alleviation from the consumption of commonly available probiotics may serve as a marker of the likelihood of any treatment response.

blood analyses were undertaken. He also had a CT scan of the pelvis and abdomen, as well as a colonoscopy and panendoscopy to rule out other possible issues that could be causing the then digestive issues. For the month prior to FMT, he was prescribed antibiotics (rifaximin 500 mg/day and vancomycin 250 mg/day), followed a low-fibre diet (less than 10 g a day), and abstained from alcohol. In the three days preceding the procedure, his diet consisted only of soup and clear liquids, and eventually became just clear liquid. The night before the procedure he completed two bowel preparations.

Next, as reported by him, "*On the morning of the FMT procedure I took three loperamide tablets and, from memory, 200 mg of valproate. I then underwent a microdacyn* [liquid antibacterial soap that removes the large intestinal biofilm] *colonic irrigation for 90 minutes, being designed to basically clear out my entire large colon.*" The specific structure of the FMT procedure is described in Box 1.

3 | RESULTS

He judged the pre-procedural colonic irrigation as initially distressing. *"It was really difficult initially. Terrible gut cramps. It felt like I'd eaten super-hot fried chicken wings and that I was expending a year's worth of waste. It filled up my large colon each time and made me feel like I was about to burst inside. At around the 45-minute mark I had to stop at one point to go to the bathroom. At around the 60-minute mark, I noticed I felt a lot calmer and much more able to tolerate the procedure. At the end of it I felt totally calm. Unbelievably calm. I felt totally clearheaded for the first time in my life, just staring at a wall. No fidgeting, no reaching for my phone, no anxious or nervous tension on the skin. Nothing."*

With regards to the first procedure itself: "*The procedure (FMT via colonoscopy) was over within the hour, and I woke up feeling like a new person. Felt amazing, like a weight had been lifted off me. Like I'd caught my breath for the first time in years. Upon waking up, I was given another dose of FMT.*"

He charted his mood states daily from initiation of FMT (22nd September 2020) until 4th January 2022 (see Figure 1). As reported by him (see Box 1), the treatment was extremely effective. He ceased valproate (200 mg/day pre-FMT) two months after the procedure and began tapering the 250 mg/day dose of quetiapine four months after commencing FMT, with complete cessation occurring after six months. At the first author's review some 12 months after initiating FMT, he was taking only 50 mg of quetiapine per day and stated that he had had no distinct highs, virtually no bipolar symptoms, and that his ADHD symptoms had improved. At a subsequent review four months later, he reported that symptom improvement had either been maintained or further improved and that he had not taken any mood stabiliser for fifteen months, nor quetiapine for four months. Figure 1 data suggest that mood episodes (while viewed by him as minor compared to the years prior to FMT) decreased in frequency and severity over the months of data recording.

4 | DISCUSSION

Single subject case studies carry obvious multiple recognised risks. When an individual reports remission or the disappearance of a clinical condition following an intensive intervention and has high expectations of the procedure, the possibility of placebo response is clearly raised.

We suggest that a placebo response can be rejected by consideration of the extensive documentation generated both by the patient and the managing clinician. A placebo response would be expected to be brief and not sustained (i.e., bipolar states would fully return

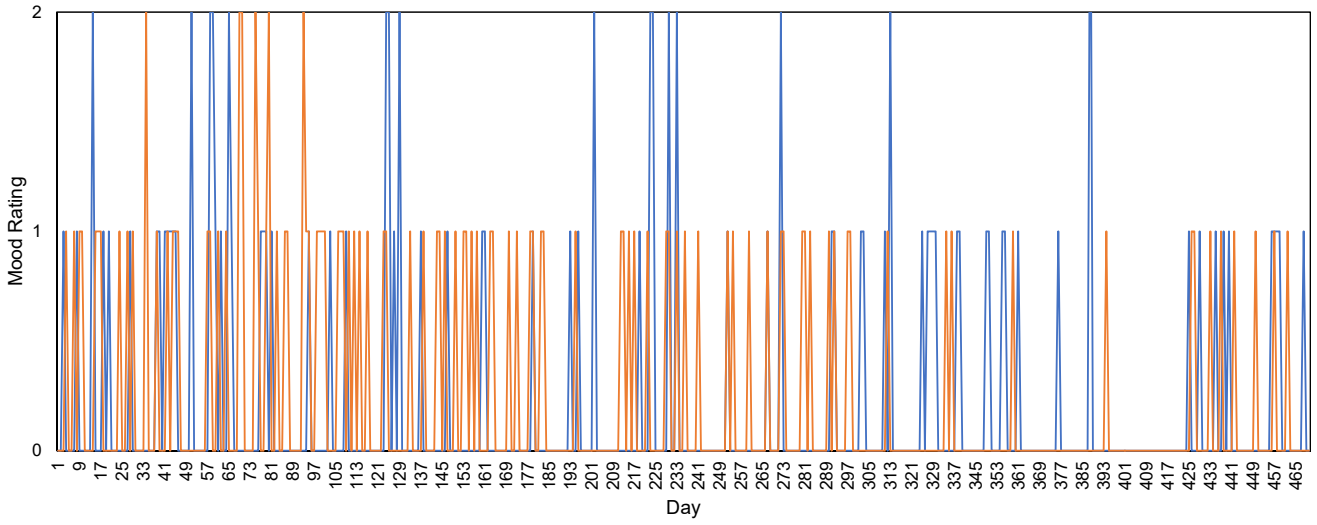

FIGURE 1 Daily ratings of depression (blue) and hypomania (orange) for the patient starting from the first day of FMT. Scores range from absent (0) to slight (1) and to mild (2) only and quantified by the participant as distinctly less severe than pre-FMT mood severity. Measurements were taken on 470 consecutive days from 22nd September 2020 until 4th January 2022.

BOX 1 Patient's description of FMT's procedural components and impact.

Procedural components

The first day of the procedure consisted of two high-dose treatments in a clinic; one via colonoscopy and the other via an enema. A second high-dose enema treatment was given on the second day. The remaining treatments were low-dose enemas completed at home. Enemas were conducted on Days 3 and 4, another five enemas were conducted over days 5–11, then four over days 12–18, three over days 19–25, two over days 26–32, one over days 33–39, and finally a fortnightly enema for the remaining time period.

Impact

"I haven't suffered full-blown hypomanic symptoms since before the procedure. There have been a few mildly high occasions but not accompanied by classic bipolar symptoms such as rapid speech, grandiosity, blowing money, impulsivity, etc. Usually, I was simply feeling good after a weekend with good friends or my girlfriend or other social events. There have been about three occasions when I suffered mild depressive episodes. One I suspect was brought on by a fish oil supplement (as depression ceased after I stopped taking it) and the other two following stressful events, but they were totally mild in comparison to the previous episodes. Incomparably. The charted 1–2 mood ratings compare with pre-FMT ratings across an 8–10 range.

I do have episodes of irritability and anxiety, but they're usually brought on by everyday life stressors or can directly be attributed to certain incidents rather than out of the blue as occurred previously.

There has been a plethora of other positive effects, so that the procedure has changed my life in many ways. My palate for foods changed immediately post-procedure. I remember distinctly craving hummus and toum [Lebanese garlic dip] *upon waking from the procedure and I have had it nearly every day since the procedure. Conversely, certain foods that I use to consume daily (e.g., vegemite, meats) I no longer touch, nor do I crave them. I no longer have intense sugar cravings, and even when I have some craving, I'm able to withstand it much better. Nighttime cravings while taking quetiapine disappeared the day of the very first dose of FMT. I was able to go without caffeine and coffee for six months shortly after FMT, having never been able to get off coffee in my life before. I'm currently the lightest I've been in the last 8 years (87kg), losing 4kg in the fortnight after the procedure, presumably reflecting an improved diet.*

My resting heart rate has also decreased massively, an average of 15–20 beats/minute. I can finally fall asleep without medication and deal with occasional sleep deprivation much better than previously. My ADHD is nowhere near as intense as it once was, and I doubt whether I meet criteria for ADHD anymore. For some reason, I don't get sunburnt as easily as previously."

after a period). In relation to the latter, he still experienced some hypomanic and depressive periods (after more than a year following the procedure), but they were both less severe and briefer. The tone of his descriptions (as provided here) is objective, contemplative, and in line with the clinician's assessment of him being an intelligent young man with a high level of insight, albeit quick to search for alternative management options to bring his condition under control.

Turning to a general appraisal, his bipolar condition had been moderately severe for a decade. Following FMT, there was a distinct improvement in mood oscillations, anxiety, and in putative ADHD symptoms, seemingly independent conditions. However, it is recognised that those who develop a bipolar condition are distinctly more likely to have anxiety disorders and even ADHD. As his generalised anxiety and panic attacks commenced at the same time as his depressive episodes emerged, some interdependencies are suggested, perhaps explaining why improvement extended beyond his bipolar disorder although independent outcome effects may also have occurred. For a man who had required extensive and extended medications to have his bipolar condition largely remit following FMT with no need for maintenance medication, such a case is quite striking.

It is unclear whether his response to FMT was idiosyncratic or not. There appear to be no signals (e.g., abnormal immunological markers, microbiome markers) for currently determining who will respond to FMT. Our patient's reporting of mood improvement after taking probiotics may be a signal and, if so, could prove to be of broad utility in screening candidates. In the protocol for a Canadian randomised controlled trial of two active FMT interventions for managing bipolar disorder,[3] the authors state that they will collect food diary information, undertake faecal microbiome profiling, analyse faecal samples for microbiome metabolomics, and undertake mucosal biopsy analyses.

His FMT procedure was extremely demanding of time, lasting nearly six months. It contrasts with the Canadian FMT bipolar study protocol,[3] where it is planned for subjects to receive only one dose of an autologous or allogenic FMT product (albeit with stool samples being collected at 12 and 24 weeks). Clearly, there is a need to determine whether the extended FMT program provided to him is necessary, or whether simpler and briefer procedures (e.g., the Canadian protocol) will suffice. Green et al.[2] note the lack of consensus about procedural aspects as well as regulatory nuances, safety issues, and side effects which are relevant in considering necessary guidelines for consideration of the procedure by patients and by clinicians.

While the patient's bipolar condition was distinctively severe to our patient, he had been able to undertake university courses, work part-time, travel overseas, and have partners and close relationships. There is a distinct percentage of individuals who have a bipolar disorder that does not respond to multiple medications, who are quite unable to work, are often housebound, and are in extreme distress. They are at distinct suicide risk, while the side effects of many of their medications risk shortening their life. There may be a case for some of these individuals to trial FMT.

ACKNOWLEDGEMENTS

This work was supported by the Australian National Health and Medical Research Council (NHMRC; grant number

GNT1176689). The contents of the published material are solely the responsibility of the individual authors and do not reflect the views of the NHMRC. Open access publishing facilitated by University of New South Wales, as part of the Wiley - University of New South Wales agreement via the Council of Australian University Librarians.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID

Gordon Parker https://orcid.org/0000-0003-3424-5519
Michael J. Spoelma https://orcid.org/0000-0003-2844-0748

REFERENCES

1. Green J, Castle D, Berk M, et al. Faecal microbiota transplants for depression – who gives a crapsule? *Aust N Z J Psychiatry*. 2019;53(8):732-734.
2. Green JE, Berk M, Loughman A, et al. FMT for psychiatric disorders: following the brown brick road into the future. *Bipolar Disord*. 2021;23(7):651-655.
3. Cooke NCA, Bala A, Allard JP, et al. The safety and efficacy of faecal microbiota transplantation in a population with bipolar disorder during depressive episodes: study protocol for a pilot randomized controlled trial. *Pilot Feasibility Stud*. 2021;7(1):142.
4. Xu H-M, Huang H-L, Zhou Y-L, et al. Faecal microbiota transplantation: a new therapeutic attempt from the gut to the brain. *Gastroenterol Res Pract*. 2021;2021:6699268.
5. Hinton R. A case report looking at the effects of faecal microbiota transplantation in a patient with bipolar disorder. *Aust N Z J Psychiatry*. 2020;54(6):649-650.