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## RESEARCH ARTICLE

# Psilocybin-Assisted Psychotherapy for Treatment-Resistant Depression in Bipolar II Disorder

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### Abstract

**Background:** Bipolar II disorder (BD-II) is often associated with chronic and treatment resistant major depressive episodes. Psilocybin has shown promise for its rapid-acting antidepressant effects, though its impact on bipolar depression remains unexplored. In the present subgroup analysis of an already published trial on treatment-resistant depression (TRD), we aimed to preliminarily evaluate the safety and efficacy of psilocybin in patients with BD-II.

**Methods:** Adults with TRD associated with BD-II, excluding those with psychosis were included. Participants underwent one or two psilocybin sessions, each with a dose of 25 mg, along with preparatory and integrative psychotherapy sessions.

**Results:** A total of four participants with a mean age of  $37.5 \pm 4.15$  years were included. At baseline, the mean Montgomery-Åsberg Depression Rating Scale (MADRS) score was 32.5 (95% CI: 26.3–38.7, SD = 3.87). By week 2 post-dose, mean MADRS decreased to 20.3, and 2 weeks after dose 2, it further dropped to 19. At the end of the 6-month study, the mean MADRS score was 21.3. Young Mania Rating Scale scores remained stable at a mean of one throughout the study with no evidence of treatment emergent mania, hypomania or psychosis observed in any participants.

**Conclusions:** These findings suggest potential improvement in depressive symptoms with psilocybin administration in BD-II. Future studies with larger sample size are required to replicate our results and further evaluate antidepressant effects of psilocybin in bipolar depression.

**Keywords:** psilocybin, bipolar II disorder, treatment-resistant depression, efficacy, psychedelics

### Introduction

Compared to bipolar I disorder, there is far less research into treatment options for bipolar II disorder (BD-II)

with quetiapine and lurasidone being the only approved medications for acute treatment of major depressive episodes (MDEs) as part of BD-II.<sup>1-3</sup> There

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are currently no evidence-based interventions for treatment resistant depression (TRD) as part of BD-II.<sup>4</sup> As such, there is an urgent need to identify and evaluate new treatment options for this population.

Scientific inquiry into the therapeutic potential of psychedelics provided a hopeful innovation paradigm shift in mental health treatment approaches.<sup>5,6</sup> Psilocybin has shown promising preliminary evidence of efficacy in alleviating symptoms across a range of mental health conditions.<sup>7–9</sup> Psilocybin-assisted psychotherapy (PAP), characterized by the administration of psilocybin in conjunction with psychotherapeutic support, has emerged as a promising modality for facilitating therapeutic insights, promoting emotional processing, and fostering existential meaning-making, thus offering a potentially transformative approach to mental health care.<sup>10</sup>

In a recently completed meta-analysis by our group, we found a large antidepressant effect size (Cohen's  $d = 0.78$ ;  $p < 0.001$ ) with PAP across 13 studies (pooled  $n = 686$ ); however, in all of these studies, history of mania or hypomania were exclusion criteria, with no studies evaluating the efficacy or safety of PAP in bipolar disorders.<sup>11</sup> Hypomania and mania have been standard exclusion criteria given concerns of potential treatment emergent mania and psychosis with psychedelic treatments. Hence, empirical testing is required to more definitively evaluate this safety concern within the context of carefully administered PAP in a supportive and medically monitored setting.

Recently, one open label pilot study was completed with 15 participants with BD-II depression finding rapid and robust antidepressant effects with PAP with no incidences of treatment emergent mania, hypomania, psychosis, or suicidality.<sup>12</sup> In addition, our group recently completed a randomized, wait-list controlled clinical trial including TRD as part of both major depressive disorder (MDD) and BD-II.<sup>13</sup> We have previously published the overall study findings; however, we did not report on the BD-II subgroup. The purpose of the present report is to provide a detailed analysis of the BD-II subgroup receiving PAP within our previous trial.

## Methods

The current randomized, wait-list—controlled clinical trial was conducted at Braxia Health in Mississauga, Ontario, Canada. Detailed descriptions of procedures and assessments are available elsewhere.<sup>13</sup> The study received Health Canada and Research Ethics Board approval (Advarra, [Pro00056530; BCDF001]), with registration on ClinicalTrials.gov (NCT05029466) completed prior to recruitment. All study procedures adhered to ethical guidelines, with written and verbal informed consent obtained from all participants.

Eligible participants, of age 18 to 75 years, were diagnosed with BD-II and experienced a MDE lasting at least 3 months at the time of enrollment. Individuals who were considered treatment-resistant, defined as not responding adequately to at least two standard pharmacological treatments, were included. Participants were required to stop certain medications, including antidepressants and antipsychotics at least five half-lives before the screening and for the duration of the trial. At the discretion of the prescribing physician and principal investigator's clinical judgment, participants with BD-II were permitted to maintain their ongoing treatment with conventional mood stabilizers during their study participation.

Participants received 25 mg of synthetic psilocybin dissolved in water, provided in-kind by the Usona Institute. They underwent preparatory, dosing, and integration therapy sessions delivered by trained professionals licensed to practice psychotherapy within Ontario. Outcome measures, such as the Young Mania Rating Scale (YMRS), the Montgomery–Åsberg Depression Rating Scale (MADRS), and the Quick Inventory of Depressive Symptoms–Self Report (QIDS-SR), were collected at specified intervals to evaluate treatment efficacy. MADRS and QIDS-SR-16 were conducted at baseline and at day 1, weeks 1–6, 8, 10, 12, 14, 16, 18, 20, 22, and 24. YMRS was conducted at baseline, pre-dose 1, post-dose 1, and post-dose 2.

The use of baseline MADRS scores, rather than those at the end of the delay period, was chosen to maintain consistency across all participants. Importantly, no significant changes in depressive symptoms were observed during the delay period, suggesting that baseline scores remained a reliable indicator of the participants' initial symptom severity.<sup>13</sup>

We utilized Statistical Package for the Social Sciences version 26 software to conduct the analysis. Baseline demographic data, such as age, sex and race were collected and summarized for all study participants. Means and percentages were calculated to describe the characteristics of study participants. We used descriptive statistics to report the mean, standard deviation, and 95% confidence intervals (CI) for changes in the MADRS, QIDS-SR-16, and YMRS outcome measures from baseline to week 2, end-of-study, and 2 weeks after dose 2.

## Results

Four participants (two female and two male; mean [SD] age, 37.5 [4.15] years) completed the baseline assessment and were included in the final data analysis. Detailed demographic and clinical characteristics of the participants are presented in Table 1. Notably, participants had a prolonged current depressive episode, with a mean duration of 15.8 (3.07) years. Out of four patients, three received two doses of psilocybin, while none

**Table 1. Study Sample Demographics at Baseline**

Characteristic	n = 4
Age, mean (SD), years	37.5 (4.15)
Female sex, %	2, 50%
Ethnicity, %	
White (Caucasian)	3, 75.0%
Arab	1, 25%
Education, %	
Bachelor's degree	3, 75.0 %
Some college/university	1, 25%
Marital status, %	
Married	1, 25%
Single	3, 75.0%
Time with depression, mean (SD), years	15.8 (3.07)
Length of current depressive episode, %	
More than 5 years	1, 25%
Between 2 and 5 years	1, 25%
Undefined	2, 50%
Secondary diagnoses, %	
GAD	2, 50%
PTSD	1, 25%
Previous medication trials, mean (SD); range	15.3 (8.26), 7–26
Previous ketamine and/or ECT treatment, %	2, 50%
MADRS at baseline, mean (SD)	32.5 (3.87)
QIDS-SR at baseline, mean (SD)	18 (4)
YMRS at baseline, mean (SD)	1 (0)

GAD, Generalized Anxiety Disorder; PTSD, Posttraumatic Stress Disorder; YMRS, Young Mania Rating Scale; MADRS, Montgomery-Åsberg Depression Rating Scale; QIDS-SR, Quick Inventory of Depressive Symptoms-Self Report.

received three doses. Although the mean MADRS score remained elevated, third doses were not administered because none of the participants met the eligibility criteria for a third dose as the clinical benefits observed from the previous doses did not justify additional intervention at that time, especially given theoretical risk of treatment-emergent hypomania in this population.

The mean MADRS score at baseline was 32.5 (95% CI: 26.3–38.7, SD = 3.87). By week 2 post-dose administration, the mean score decreased to 20.3 (95% CI: –0.674 to 41.2, SD = 13.15), and at week 2 of dose 2, it further decreased to 19 (95% CI: 7.00–35.5, SD = 10.58). At the end of the study, the mean MADRS score was 21.3 (95% CI: 7.00–35.5, SD = 8.96). These findings suggest a potential trend towards improvement in depressive symptoms with psilocybin administration (Fig. 1). Figure 2 indicates mean MADRS score changes for each participant. Furthermore, we examined the impact of psilocybin on QIDS-SR scores across various time points. At baseline, the mean QIDS-SR score was 18.0 (95% CI: 11.6–24.4, SD = 4.00). By week 2 post-dose administration, the mean score decreased to 10.3 (95% CI: –5.03 to 25.5, SD = 9.60). At week 2 of dose 2, the mean score was 10.0 (95% CI: –4.90 to 24.9, SD = 6.00). At the end of the study, the mean QIDS-SR score

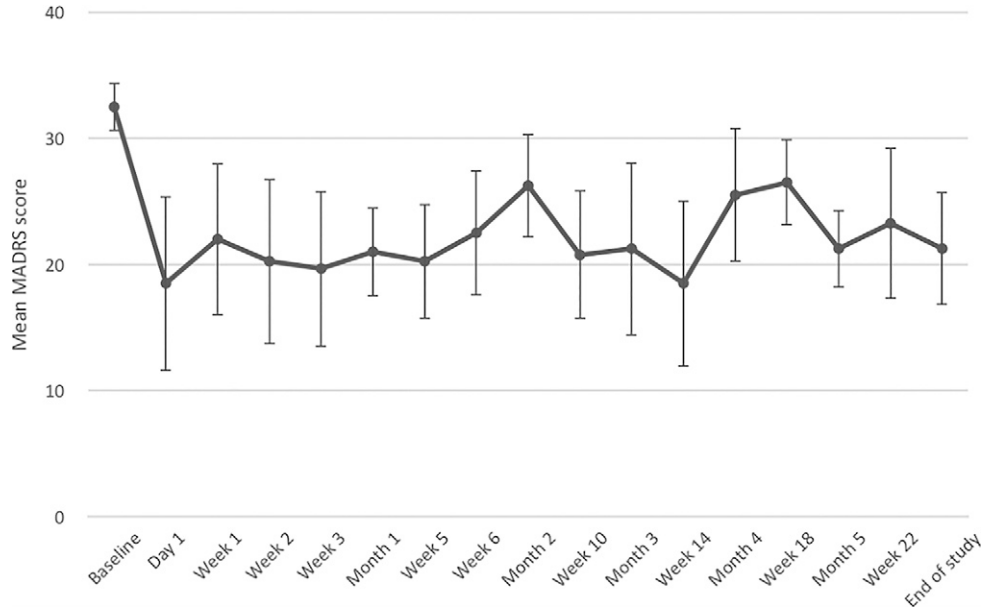
was 15.7 (95% CI: 12.8–18.5, SD = 1.15). These results indicate potential changes in QIDS-SR scores with psilocybin administration. Lastly, we examined YMRS scores at baseline, pre-dose 1, post-dose 1, and post-dose 2. Across these time points, YMRS scores consistently showed a mean of 1 (95% CI: 1 to 1, SD = 0), indicating stable manic symptomatology throughout the study phases.

## Discussion

Our trial results align with previous research demonstrating the efficacy of psilocybin in treatment of BD-II.<sup>12,14,15</sup> Aaronson et al. conducted a 12-week open-label trial involving 15 participants resistant to conventional treatments.<sup>12</sup> They received a single 25 mg dose of synthetic psilocybin, leading to significant reductions in depressive symptoms measured by the MADRS scale across all post-treatment evaluations. Secondary measures, including self-reported depression symptoms and quality of life, also showed improvements. In contrast, Morton et al. conducted an international web-based survey study on psilocybin use in BD, revealing mixed outcomes among 541 respondents.<sup>15</sup> While some reported exacerbation of symptoms such as mania and anxiety, serious adverse events requiring emergency medical attention were rare. Despite challenges, many participants perceived psilocybin as more beneficial than harmful for their mental health.<sup>15</sup> Furthermore, it is essential to note that the experiences and findings from this study cannot be directly extrapolated to patients with bipolar I disorder, as the pathophysiology and treatment responses may differ significantly between BD-II and BD-I.

Our study, which observed no induction of manic episodes following psilocybin administration, contrasts with reports from other research where individuals with BD experienced exacerbation of manic symptoms post-psilocybin use.<sup>16</sup> This discrepancy may be attributed to our controlled environment and meticulous participant selection, which likely minimized risks through stringent monitoring and structured therapeutic protocols. The moderate, single dose of psilocybin administered under controlled conditions in our study may have contributed to these distinct findings compared with less controlled settings reported in previous studies. The variability in BD symptomatology and individual responses to psilocybin underscore the necessity for personalized treatment approaches and rigorous monitoring in future research and clinical applications involving psychedelics in BD management.

The comparison between anecdotal data and our findings illustrates the critical role of rigorous methodology in clinical research. Anecdotal reports may offer initial insights, but they lack the systematic evaluation necessary for drawing robust conclusions. Our study provides a structured approach that can better inform clinical

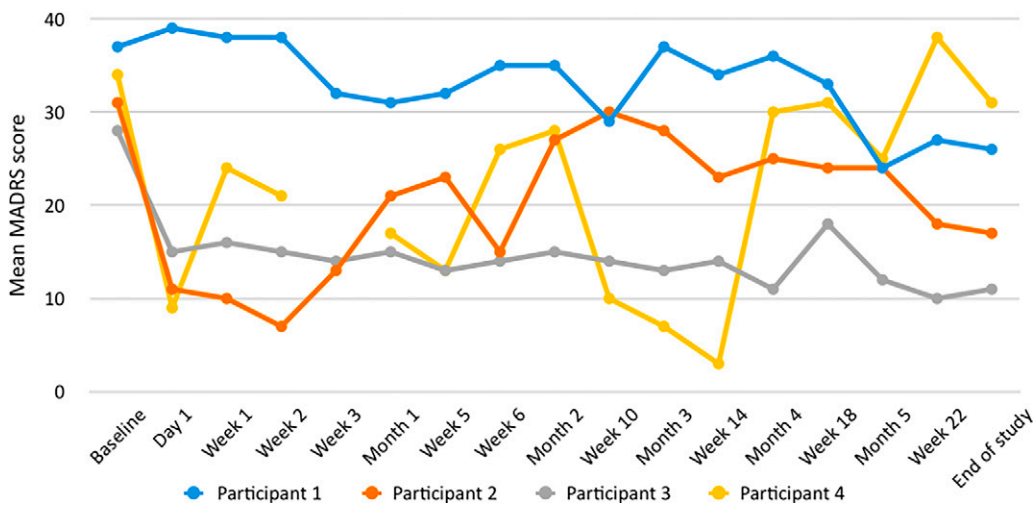


**Fig. 1.** MADRS score for all participants during the course of trial. Depression severity changes using the mean clinician-rated depression scale (MADRS) and standard error (SE).

practice and future research. Moreover, the results from our study emphasize the need for additional research that prioritizes systematic methodologies to validate or refute anecdotal claims. By grounding our findings in rigorous experimentation, we contribute valuable data to the ongoing discourse on psilocybin’s therapeutic potential.

The present study has several significant limitations. These include an open-label design and a small sample size potentially biasing towards larger antidepressant effects. The heterogeneous nature of the sample both

strengthens and weakens the study, affecting observed outcomes. This variability, combined with the aforementioned methodological constraints, precludes direct regulatory implications for psilocybin in treating BD-II. However, this diversity was deliberately chosen to enhance real-world applicability. In addition, the study did not assess participant expectancy, a known factor influencing therapeutic outcomes. Another notable limitation is the modification of critical study aspects compared with previous trials, such as including participants



**Fig. 2.** MADRS score changes during the course of trial for each participant.

with more complex psychiatric histories, reducing preparatory and integration psychotherapy, and testing repeated psilocybin doses.

In conclusion, this study indicated the potential antidepressant effects of PAP in individuals with BD-II. We found significant reductions in depressive symptoms, highlighting a therapeutic benefit. Importantly, no hypomanic switch or breakthrough hypomania was observed, underscoring the safety of psilocybin over the 24-week follow-up period—a suitable duration for monitoring BD-II. Further research is needed to validate these findings and explore the safety and efficacy of psilocybin in BD.

### **Ethics Approval and Consent to Participate**

The study received Research Ethics Board approval (Advarra, [Pro00056530; BCDF001]). All participants provided a written consent form.

### **Consent for Publication**

Not applicable.

### **Availability of Data and Material**

As a small, single-center study with study data consisting of sensitive, confidential medical records, our dataset is not publicly available and has not been uploaded to any repositories. Importantly, we did not have ethics approval for data sharing; data sharing (with individuals outside of our research group) was not included in the informed consent form. As such, we are unable to share our raw data or upload to any public repositories. However, our group remains open to collaborations for scientists requesting new types of analyses. Accordingly, upon request to the corresponding author, summary statistics on data collected can be made available for other researchers. Similarly, researchers may recommend and conduct new analyses on our existing dataset in collaboration with the corresponding author. Any data requests should be made in writing to the corresponding author via email and will be evaluated on a case-by-case basis based on compliance with research ethics approval and scientific validity of the requested type of analysis. The paper does not report original code. Any additional information required to reanalyze the data reported in this paper is available from the Dr Rosenblat upon request.

### **Authors' Contributions**

J.D.R. was the principal investigator responsible for study conceptualization, funding acquisition, investigation, methodology, project administration, and supervision. S.M., Z.D., E.K., and R.B. contributed to study conceptualization, investigation, methodology, project administration, and writing—reviewing and editing.

S.M. also contributed to formal analysis and writing the first draft. F.A.G., M.G.B. and G.W. were study therapists contributing to study conceptualization, investigation, methodology, and writing—reviewing and editing. R.S.M. was the study sponsor contributing to study conceptualization, methodology, project administration, supervision, and writing—reviewing and editing. R.B.M. contributed to writing—reviewing and editing.

### **Author Disclosure Statement**

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