Conceptual Study Proposal

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Title: An Open Label Study of Single-Dose Psilocybin for Major Depressive Disorder with co-occurring Borderline Personality Disorder

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Background: A major complication to recovery from major depressive disorder (MDD) is when it co-occurs with borderline personality disorder (BPD). Borderline personality disorder is characterized by mood instability, cognitive symptoms, impulsive behavior, and disturbed relationships (1–3). A variety of psychotherapies have been developed (4–6) and, while research on the use of medication is ongoing, no drug has been approved in the United States or elsewhere for its treatment (7). Second generation antipsychotics have been the most intensively studied (8–11). Current treatments for BPD are often inadequate. Dialectical behavioral therapy has been shown to reduce BPD but finding trained psychologists is difficult. Thus, treatments for MDD are often inadequate when BPD is present and no antidepressant has shown benefit for BPD. Thus, treatment strategies that target both MDD and BPD are needed.

Study Objectives: The primary objective of the proposed study is to evaluate the safety and efficacy of psilocybin in adults with major depressive disorder (MDD) and borderline personality disorder (BPD). Ten subjects with MDD and BPD will receive a single 25 mg oral dose of psilocybin. The hypothesis to be tested is that psilocybin will result significant reduction in symptoms of both MDD and BPD after 1 week and sustained for 4 weeks compared to baseline (improvement in symptoms will be indicated by lower scores on established outcome measures of MDD and BPD symptoms that have been used in prior studies).

Methodology: Ten individuals with major depressive disorder (MDD) and borderline personality disorder (BPD) will be recruited for an open label study in which a single dose of psilocybin is administered. All 10 subjects will have current MDD and BPD per DSM-5 criteria. One week following baseline visit (visit 1), subjects will receive a single 25 mg oral dose of psilocybin (visit 2). Participants will be seen for follow-up 1 and 2 weeks following administration and then 4 weeks following administration (visit 5).

Study Population/Sample Size: 10 male and female outpatients aged 18-65 with a current diagnosis of MDD and BPD.

Inclusion criteria:

1) Age 18-65

2) Diagnosed with current major depressive disorder

3) Montgomery-Asberg Depression Rating Scale (MADRS) score of $\geq$ 20

4) Diagnosed with borderline personality disorder

5) Borderline Personality Disorder Symptom Assessment Scale (BPD-SAS)) score of $\geq$ 20

4) Ability to understand and sign the consent form

Exclusion criteria:

1) Unstable medical illness based on history or clinically significant abnormalities on baseline physical examination

2) Current pregnancy or lactation, or inadequate contraception in women of childbearing potential

3) Illegal substance use based on urine toxicology screening (except cannabis use)

4) Current or past history of bipolar I disorder, schizophrenia, or schizoaffective disorder

5) Active substance use disorder

6) Subjects considered an immediate suicide risk based on the Columbia Suicide Severity Rating Scale (C-SSRS)

7) Use of any new psychotropic medication started within the last 3 months prior to study initiation

8) Current treatment with ketamine or esketamine

9) Cognitive impairment that interferes with the capacity to understand or provide written informed consent

Drugs, Dosages, and Regimens: All subjects who are enrolled will receive a single 25 mg oral dose of psilocybin at visit 2. Subjects will be seen weekly for the first 2 weeks following administration and for a final visit 4 weeks following administration.

Diagnostic Evaluation: Psychiatric evaluation using the major depressive episode and borderline personality disorder modules of the Mini International Neuropsychiatric Interview (MINI).

Assessments: Those subjects who appear appropriate for the study, based on telephone screening, will be invited for an in-person baseline assessment (visit 1). The duration of the baseline assessment will be approximately 90 minutes and will include the following: Informed consent, demographic data, a full psychiatric evaluation with assessment of concomitant

medications, family history, and medical evaluation including measurement of weight and vital signs, physical examination, electrocardiogram, urine pregnancy test (for women of childbearing years), urine drug screen, and liver function test; other measures include: Montgomery-Asberg Depression Rating Scale (MADRS), Borderline Personality Disorder Symptom Assessment Scale (BPD-SAS) Columbia-Suicide Severity Rating Scale (C-SSRS), Clinical Global Impression – Severity scale (CGI-S), and cognitive tests assessing attention and psychomotor speed, executive function, memory, and emotion and social cognition using the Cambridge Neuropsychological Test Automated Battery (CANTAB).

Visit 2 will entail MADRS, BPD-SAS, CGI-S, C-SSRS, and all participants will receive the dose of psilocybin and be monitored for acute response and safety (adverse events). Other follow-up visits (visit 3 and visit 4) will be held virtually and will include assessment of adverse events, MADRS, BPD-SAS, C-SSRS, CGI-S, and Clinical Global Impression – Improvement scale (CGI-I).

The final visit (visit 5) will be in person and will include assessment of adverse events, repeat medical evaluation including measurement of weight and vital signs, physical examination, electrocardiogram and liver function test as indicated; other measures include: MADRS, BPD-SAS, C-SSRS, CGI-S, CGI-I, and cognitive tests assessing attention and psychomotor speed, executive function, memory, and emotion and social cognition using CANTAB.

Efficacy: The co-primary outcome measure will be the change in MADRS score and BPD-SAS score from Visit 2 (dosing visit) to post-dose week 4. The secondary outcome measures will be the change in CGI-S and CGI-I scores from Visit 2 to post-dose week 4 and change in CANTAB test scores from baseline to post-dose week 4. Percentage of "responders" at each visit will be a secondary outcome measure. Response will be defined a priori as a score of 1 or 2 on the CGI Improvement Scale ("very much improved" or "much improved").

Timeline of Visits

Assessment	Dosing	Follow-up	Follow-up	Final Visit
Week 0	Week 1	Week 2	Week 3	Week 5
Visit 1	Visit 2	Visit 3	Visit 4	Visit 5
All severity measures plus CANTAB	All severity measures	All severity measures	All severity measures	All severity measures plus CANTAB

Data Analysis:

In all efficacy analyses, only subjects who return for one visit after taking psilocybin will be included. Primary analysis will use a last observation carried forward approach. Variables that were collected at baseline and final visit will be analyzed using a paired *t* test or the nonparametric Wilcoxon test. The nonparametric Cochran Q test will be used to analyze the binary responder variable. The remaining variables will be analyzed using a repeated measures general linear model (GLM) analysis with polynomial contrasts across the repeated visits.

Changes in cognitive performance between baseline and end of treatment will be assessed in subjects using paired *t* tests. Performance of subjects at baseline and at study end point will be compared separately to baseline data from healthy volunteers using unpaired *t* tests.

This being a pilot study, all tests of hypotheses used a significance level of 0.05.

Sample Size:
This being a proof of concept study, 10 participants should be sufficient to detect a signal and allow for future studies to be appropriately powered.

Safety/Tolerability: Safety and tolerability will be assessed using health and safety measurements data, spontaneously reported side-effects and adverse events data, and premature termination data.

During psilocybin dosing at Visit 2, two monitors will be present with the patient at all times during dosing. The PI or sub-I (both board certified psychiatrists) will serve as the lead monitor and a clinical research coordinator (possessing a Bachelor's degree in psychology with 2+ years of working in a licensed mental health care setting) will serve as the assistant monitor.

The psilocybin administration session at Visit 2 will generally last ~6–8 hours. The first effects of psilocybin should be seen about 20–30 min after administration, are most intense in the first 90–120 min and then gradually subside, typically resolving in ~5−6 h after administration. After at least 6 h, once the effects of the study drug have mostly subsided, participants will be assessed for safety by the clinical judgement of a psychiatrist. The participant will then be released into the care of a friend or family member.

Baseline health and safety measures will be assessed at the initial visit and will include assessment of weight and vital signs, physical examination, electrocardiogram, urine pregnancy test, urine drug screen, and liver function test and will be repeated at the final visit as indicated.

Follow-up visits will include assessment of safety measures including side-effects and adverse events as well as suicidality. Subjects who are an immediate suicide risk will be removed from the study and appropriate clinical intervention (e.g. hospitalization) will be arranged. Subjects will also be provided with a phone number to reach the PI in case of a physiological or psychological emergency. The PI will be on call at the provided number at all times (24/7) for the duration of the study.

Subject Withdrawal:

If a subject withdraws from the study, all instruments administered at the screening visit will be completed at the final visit. These will be conducted when the subject is able to come in for an early termination visit. Withdrawn subjects will be given the phone number of the principal investigator as well as the phone numbers of local resources for depression treatment.

Adverse Event Reporting:

Unanticipated (unexpected) problems/events, those that are *not* already described as potential risks in the consent form, or *not* part of an underlying disease, will be reported to the IRB as soon as possible. The same will be done for serious problems/events and, in the opinion of the investigator, are possibly, probably or definitely related to the research procedures. A follow-up report will also be submitted to the IRB with any documentation related to a previously submitted adverse event.

Enrollment Timeline: 12 months from first subject to last subject enrolled.

Publication Plan: These data will be presented at the American College of Neuropsychopharmacology (ACNP) annual meeting, the American Psychiatric Association (APA) annual meeting, or the American Society of Clinical Psychopharmacology (ASCP) annual meeting. The resulting article will be submitted to a peer-reviewed publication (e.g., American Journal of Psychiatry, Biological Psychiatry) within 3 months of study completion.

Estimated Budget: NA

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