The Neurobiological Effects of Psilocybin in Treatment Resistant Bipolar Depression: Protocol and Interim Analysis of an Emotional-Processing fMRI Pilot Study

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Submitter Erica Kaczmarek

Affiliation University of Toronto

SUBMISSION DETAILS

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Abstract: Background: Bipolar Disorder (BD) is a severe and persistent mental illness with a lifetime prevalence of 2-3%. Individuals with BD spend a significant portion of their lives experiencing depressive episodes, yet bipolar depression remains a considerable treatment challenge. Current pharmacological treatment options are limited and are often associated with significant adverse effects. Treatment outcomes for bipolar depression are poor, with approximately one-third of patients failing to respond to two or more first-line treatments (i.e., treatment resistant bipolar depression (TRBD)). Consequently, there is an urgent need to develop novel therapeutics for bipolar depression, although progress is hindered by our limited understanding of the neurobiology of BD.
Methods: Participants (n=20) with a primary diagnosis of Bipolar II Disorder will receive a single 25 mg oral dose of psilocybin with accompanying psychotherapy (PAP) as part of an ongoing open-label clinical trial. Eligibility criteria includes a current moderate to severe major depressive episode failing two or more adequate treatment trials. The primary outcome is to evaluate neurobiological effects of psilocybin by examining the association between post-treatment right amygdala activity, measured via a facial affect task during an fMRI, and antidepressant effects over time. We hypothesize the increased right amygdala activity in response to emotional stimuli one day after psilocybin treatment will correlate with greater antidepressant effects in the one-week period post-treatment in individuals with TRBD, as seen in unipolar TRD samples. The trial was registered on ClinicalTrials.gov (NCT06506019).
Results: Enrollment for the study opened on November 25, 2024. Recruitment for the trial is ongoing (n=6 enrolled to date) with an expected recruitment rate of 2 participants per month. An interim analysis will be completed in May 2025 (prior to the conference), which will include evaluation of antidepressant effects, tolerability, and adverse events for all participants enrolled to date.
Conclusions: This presentation will provide an overview of a novel trial investigating PAP for TRBD. To date, only two small pilot trials have included participants with Bipolar II Disorder (with n=19 BD

participants in total), making this research a critical contribution to the field. Furthermore, the incorporation of neuroimaging offers a unique opportunity to elucidate both the pathobiology of bipolar depression and the neurobiological effects of psilocybin.

Learning Objectives:

Learning Objective 1 Describe the proposed neurobiological mechanisms of psilocybin.

Learning Objective 2 Evaluate psilocybin-assisted psychotherapy as a novel avenue of treatment for bipolar II depression.

DISCLOSURE

Financial Relationships

Disclosure No, I have nothing to disclose.