John Hutchison

EDPS 643

Final Project

Research Proposal: Investigating the Effectiveness of Psilocybin in Treating Depression

**Part 1: Literature Review and Framing the Question**

*1.1 Introduction*

Depression is a debilitating mental health disorder affecting millions worldwide. Traditional treatments, including antidepressants and psychotherapy, have varying degrees of success, often accompanied by significant side effects and relapse rates. Recently, there has been a resurgence of interest in the potential therapeutic benefits of psychedelics, such as psilocybin, LSD, and MDMA, for treating mental health disorders, including depression.

Preliminary studies have shown that psychedelics may have rapid and sustained antidepressant effects. This research proposal aims to investigate the effectiveness of psilocybin in treating depression, providing a comprehensive understanding of its potential as alternative or adjunctive therapies.

*1.2 Key Research Points*

* Psilocybin and Treatment-Resistant Depression:
* An open-label feasibility study demonstrated significant reductions in depression severity with psilocybin treatment, with sustained effects for up to three months post-treatment. Psychological support was crucial for positive outcomes (Carhart-Harris et al., 2016).
* Psilocybin for Depression and Anxiety in Cancer Patients:
* A randomized double-blind trial found substantial and sustained decreases in depression and anxiety among patients with life-threatening cancer, indicating the therapeutic potential of psilocybin in severe medical conditions (Griffiths et al., 2016).
* Quality of Psychedelic Experience:
* Positive acute psychedelic experiences, characterized by mystical-type effects, were predictive of better therapeutic outcomes in treatment-resistant depression, emphasizing the importance of the subjective experience (Roseman et al., 2018).
* Psilocybin for Tobacco Addiction:
* A pilot study on psilocybin for tobacco addiction showed significant potential for substance use disorders, with positive outcomes suggesting broader applications, including depression treatment (Johnson et al., 2014).
* Pharmacology of Psychedelics:
* Detailed review of the pharmacology of psychedelics such as psilocybin, LSD, and MDMA, providing foundational knowledge on their mechanisms of action, safety profiles, and therapeutic applications (Nichols, 2016).
* Ayahuasca and Rapid Antidepressant Effects:
* A randomized placebo-controlled trial found rapid and significant antidepressant effects of ayahuasca in patients with treatment-resistant depression, contributing to the evidence for psychedelic efficacy (Palhano-Fontes et al., 2019).
* LSD-Assisted Psychotherapy for Anxiety:
* A qualitative study on LSD-assisted psychotherapy for anxiety in patients with life-threatening diseases showed acute and sustained anxiety reductions, suggesting broader therapeutic potential (Gasser et al., 2015).
* Emerging Psychopharmacological Therapies:
* Review of clinical trials and potential benefits of psilocybin and MDMA in treating psychiatric disorders like depression and PTSD, emphasizing the need for continued research and regulatory consideration (Mithoefer et al., 2016).

*1.3 Research Question(s)/Hypotheses*

Primary Research Question:

* How effective is psilocybin in reducing symptoms of depression compared to a placebo?

Primary Hypothesis:

* Participants receiving psychedelic treatment will show a greater reduction in depression severity, as measured by the Montgomery-Asberg Depression Rating Scale (MADRS), compared to participants receiving a placebo.

Secondary Research Question:

* How long do the antidepressant effects of psychedelics last post-treatment?

Secondary Hypotheses:

* The antidepressant effects of psychedelics will be sustained for at least three months post-treatment.

*1.4 References*

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Mithoefer, M. C., Grob, C. S., & Brewerton, T. D. (2016). Novel psychopharmacological therapies for psychiatric disorders: Psilocybin and MDMA. The Lancet Psychiatry, 3(5), 481-488.

Nichols, D. E. (2016). Psychedelics. Pharmacological Reviews, 68(2), 264-355.

Palhano-Fontes, F., Barreto, D., Onias, H., Andrade, K. C., Novaes, M. M., Pessoa, J. A., ... & Hallak, J. E. (2019). Rapid antidepressant effects of the psychedelic ayahuasca in treatment-resistant depression: a randomized placebo-controlled trial. Psychological Medicine, 49(4), 655-663.

Roseman, L., Nutt, D. J., & Carhart-Harris, R. L. (2018). Quality of acute psychedelic experience predicts therapeutic efficacy of psilocybin for treatment-resistant depression. Frontiers in Pharmacology, 8, 974.

**Part 2: Research Methods and Design**

*2.1 Study Overview with Classification*

This study will be a double-blind, randomized, placebo-controlled trial, making it an experimental study. Participants will be randomly assigned to either the treatment group (receiving psilocybin) or the control group (receiving a placebo). This random assignment helps to eliminate selection bias and ensures that the groups are comparable at the start of the experiment.

*2.2 Sampling Plan*

The target population will be adults aged 18-65 diagnosed with major depressive disorder (MDD) according to DSM-5 criteria. Participants will be recruited through multiple channels, including advertisements in mental health clinics, online platforms, community centers, and referrals from healthcare providers. Potential participants will undergo a screening process to determine eligibility based on inclusion and exclusion criteria. Exclusion criteria include history of psychotic disorders or bipolar disorder, current substance abuse or dependency, pregnant or breastfeeding women, and use of medication or treatments that could interfere with the study.

The sample size will be calculated based on a power analysis to detect a clinically significant difference in depression severity between the treatment and control groups. This calculation will consider expected effect sizes, desired power (typically 0.80), and significance level (typically 0.05). The final sample size will depend on the number of eligible participants interested in being involved but should include at least 100 (50 per group) to ensure sufficient power.

Participants will be randomly assigned to either the psychedelic treatment group or the placebo control group using a computer-generated randomization sequence. Randomization will be stratified by baseline depression severity to ensure balance between groups.

* 1. *Study Variables and Measures*

The independent variable in this study is psychedelic treatment. This variable represents whether the participant receives the psychedelic treatment or the placebo. The psychedelic used (psilocybin) and its dosage will be standardized across the treatment group.

There are two dependent variables in this study: depression severity and duration of antidepressant effects. Depression severity will be measured using the Montgomery-Asberg Depression Rating Scale (MADRS). This scale assesses the severity of depressive episodes with scores ranging from 0 to 60, where higher scores indicate more severe depression. The duration of antidepressant effects will be evaluated through follow-up assessments of depression severity at 3-, 6-, and 12-months post-treatment using the MADRS.

The covariates in this study include:

* + Baseline Depression Severity: Initial MADRS scores to ensure comparability between groups.
  + Demographic Variables: Age, gender, socioeconomic status, and education level.
  + Medication Use: Record of any concurrent medications that participants are taking.
  + Psychological Support: The level and type of psychological support provided during and after the psychedelic experience.

*2.4 Procedure*

The study will begin with a preparation phase (months 1-3), involving protocol development, obtaining ethics approval, and staff training. Recruitment and screening (months 4-6) will involve advertising through various channels and conducting initial phone or online screenings followed by in-person or virtual assessments to confirm eligibility. Participants who meet the inclusion criteria will provide informed consent and undergo baseline assessments, including the MADRS and demographic and medical history questionnaires. Participants will then be randomly assigned to either the psychedelic treatment group or the placebo group using a computer-generated randomization sequence, with stratification by baseline depression severity to ensure balance.

During the intervention phase (months 7-9), participants in the psychedelic group will receive the treatment (psilocybin) in a controlled setting with standardized dosage and administration, while the placebo group will receive a placebo under the same conditions. Psychological support will be provided to all participants during and after the session, including preparation and integration sessions. Immediately post-treatment, participants will undergo another MADRS assessment.

Follow-up MADRS assessments will be conducted at 6 weeks, 3 months, 6 months, and 12 months post-treatment. Adverse events will be monitored and recorded throughout. Data will be analyzed using mixed-effects models and intention-to-treat analyses to account for repeated measures. In this model, the fixed effects will include treatment group, time, and the interaction between treatment and time. The random effects will include participant effects and random intercepts and slopes. Mixed-effects models are robust to missing data points and increase statistical power by accounting for within-subject correlation, making it a suitable analysis method for this study.

*2.5 Validity Considerations*

Internal Validity Considerations:

Selection bias may occur if there are differences between the treatment and control groups that are not due to the treatment itself. To mitigate this, random assignment will be used to ensure that participants are equally likely to be assigned to either the treatment or control group, and the randomization will be stratified by baseline depression severity.

Another internal validity concern is attrition. Due to the longitudinal nature of the study, differential dropout rates between the treatment and control groups may bias the results. To mitigate this, strategies will be implemented to enhance retention, including regular follow-up communication.

Lastly, potential confounding variables such as concurrent medications and psychological support will be adjusted for during the analysis phase.

External Validity Considerations:

The main external validity concern in this study regards the ecological validity. The controlled setting of the study may not reflect real-world conditions in which the broader population exists. To increase the robustness of this study and enhance the generalizability of the results, follow-up studies should be conducted in more naturalistic settings.

**Part 3: Answering the Question**

*3.1 Results/Findings*

The results of this study demonstrated a significant reduction in depression severity among participants receiving psychedelic treatment compared to those receiving a placebo, as measured by the MADRS. Participants in the psychedelic group showed significant improvement in depressive symptoms immediately post-treatment (SE = -10, p=0.001), with sustained benefits observed at follow-up intervals of 6 weeks, 3 months, 6 months, and 12 months. The interaction term between treatment and time yielded a significant result (SE = 0.3, p=0.001), suggesting that the treatment group experienced greater improvement in depression severity over time than the control group. The mixed-effects model explains a substantial portion of the variability in depression severity. The fixed effects alone account for 45% of the variability, while including the random effects increases the explained variance to 65%.

*3.2 Conclusions*

This study aims to build on the growing body of literature that highlights the potential of psychedelics in treating depression. Previous research has provided promising evidence of the rapid and sustained antidepressant effects of psychedelics. By employing a rigorous double-blind, randomized, placebo-controlled design, my study seeks to address some of the limitations of earlier research and provide more definitive conclusions regarding the efficacy and safety of psychedelic treatments. Overall, the findings provide robust evidence supporting the efficacy and safety of psychedelics as a novel treatment for major depressive disorder, paving the way for further research and potential clinical applications.