Effect of Psychedelic (LSD and Psilocybin) Use in Treating Mental Disorders like Major Depressive Disorder (MDD)

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Abstract – *Major Depressive Disorder (MDD) is a widespread problem throughout the United States with no shortage of treatments. Psilocybin, a serotonin agonist, is treatment for MDD that showed great potential but wasn't explored much until recently. Psilocybin, when administered in micro doses along with therapy, showed great curative potential for MDD, ameliorating symptoms for long periods of time. Psilocybin has also shown to work quickly and was not addictive to the patients. This review looks at studies testing psilocybin as a treatment for MDD.*

keywords – *major depressive disorder, psilocybin, LSD, psychedelics, serotonin 2A agonists, ayahuasca, post-traumatic stress disorder*

I. Introduction

Depression is a mental disorder that effects one in fifteen adults every year and one in six adults over their lifetimes [7]. Depression is characterized by feeing sad or depressed, losing interests in hobbies, changes in appetite, and even thought of death or suicide [7]. There are other associated symptoms which can also manifest under the guise of other medical issues such as thyroidism and vitamin deficiency [7].

Current treatment for depression is talk therapy and anti-depressant drugs. However, there is little knowledge into the efficacy of these drugs and their side effects aren't negligible [8]. It is important to note that while depression therapeutics might alleviate symptoms of depression, there is always the risk of recurrence as treating the symptoms does not equal treating the illness [8].

Furthermore, a large population of individuals with major depressive disorder (MDD) might also suffer from post-traumatic stress disorder (PTSD). Approximately half of the individuals with PTSD also suffer from MDD [9]. Treating PTSD is similar to treating MDD where alleviating symptoms does not mean that the illness is cured. Currently, the regulation for treating PTSD set by the Veterans Health Administration (VA) and Department of Defense (DoD) have worked in treating the symptoms of PTSD on a highly personalized level and needed further research into more effective treatment for a more generalized population of PTSD sufferers and for a more diverse population [9].

Prior to the Nixon era war on drugs, research investigated using psychedelics to treat disorders like depression and PTSD. Nixon's war on drugs cut funding into this research and started the association of psychedelics with anti-establishmentarianism and the belief that psychedelics stopped brain growth [10]. However, in the last 10 years, research into the effect of psychedelics on depression and PTSD is being renewed, with even an FDA Phase 3 trail with 50 participants investigating MDMA as a treatment for veterans with PTSD and depression [11].

This literature review will aim to look at studies that have been done on depression using LSD or other psychedelics.

II. Depression

Lysergic Acid Diethylamide (LSD) is a substance which causes changes in perception, mood, and cognitive processes, originally discovered, and ingested by Albert Hofmann [1,2,12]. LSD, DMT, Psilocybin and other psychedelics are serotonin 2A receptor agonists which means they have been found to have similar chemical structurers to serotonin, a neurotransmitter [3,4]. The current treatment for depression is Selective Serotonin Reuptake Inhibitor (SSRI)'s, which also act as 5-HT receptors, indicating that psilocybin and SSRI's have a similar function [18].

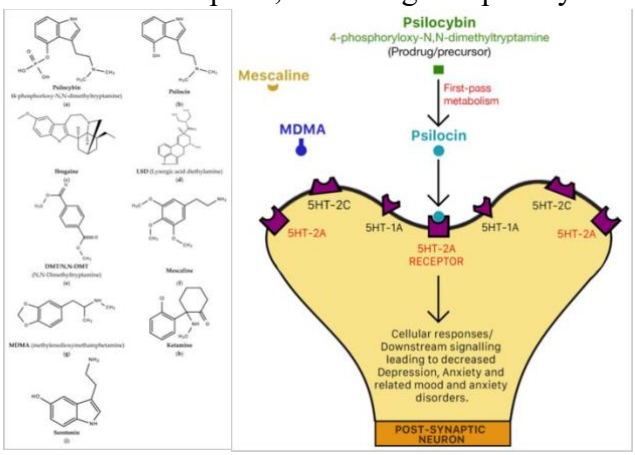

Figure 1. LEFT: (a) shows Psilocybin, a serotonin 2A receptor agonist, (b) shows Psilocin, a dephosphorylated active metabolite psilocybin [16,17], (i) shows serotonin, a neurotransmitter. Both use the 5HT-2A receptor [16]. RIGHT: The image shows psilocybin phosphorylating into psilocin which then binds to the 5HT-2A receptor [16].

Studies have into depression have put forth the "monoamine theory of depression" which postulate that depression is caused by the lack of serotonin, dopamine, and/or norepinephrine [5]. Studies have been done to show that using psilocybin or DMT have consistently reduced symptoms of depression, anxiety, and post-traumatic stress disorder. The monoamine theory was used as a basis for many following studies, either to consider it outdated, or to lean into it. Idell et al. moved past the monoamine theory of depression by targeting the fibrinolytic system, where they had found a link between depression and aberrant extravascular fibrin [19]. The study looked at how tissue plasminogen activator (tPA) regulates the synaptic plasticity and neurogenesis through BDNF activation. BDNF activation would be lowered by the binding of plasmin and tPA during brain inflammation, leading to depression. The study postulated that psilocybin would decrease the symptoms in depression from the aberrant extravascular fibrin, by inhibiting TNF-a, a cytokine which inhibit the fibrinolytic system [19]. A parallel-arm double blind placebo-controlled experiment testing the antidepressant effects of ayahuasca (a plant with DMT), had remission rates much higher than the control group at 35% versus 7% [6].

This shows that in a controlled environment, psychedelics drugs like DMT, LSD, and Psilocybin can have a curative effect on depression. However, there are limits on this effect. It has been posited that the curative effect is largely dependent on the psychedelic experience itself, rather than the receival [13]. This is partially thought to be accredited to the micro-dose of the psychedelic which is more subperceptual and cannot induce a psychedelic episode [14]. Furthermore, subjects of psychedelic testing are not dosed in a vacuum; psychedelic doses are bookended by rigorous psychological treatment [13].

A study done by Roseman et al. considered psilocybin as a treatment for treatment resistant depression [13]. Participants were given 10 mg of psilocybin and 25 mg of psilocybin a week apart. Before the first dose, participants underwent preparation sessions with a therapist; after the second dose, participants have sessions with the therapist 1-day and 1-week after the 25 mg dose. While the participants were experiencing the effects of the psilocybin, they were placed in calming environment with calming music pre-selected by the researchers. The 16-item Quick

Inventory of Depressive Symptoms (QIDS-SR16) was used as the measurement metric and was administered at 5 weeks. Compared to the baseline measurement, the findings were considered statistically significant [13].

In a pilot study aimed at evaluating the efficacy of psilocybin as a treatment for depression, researchers followed subjects for an extended period, during which subjects experienced a baseline depression screening, follow up screening, 2 doses of psilocybin, and 3 month follow ups assessing their mental state using the QIDS-SR16 [15].

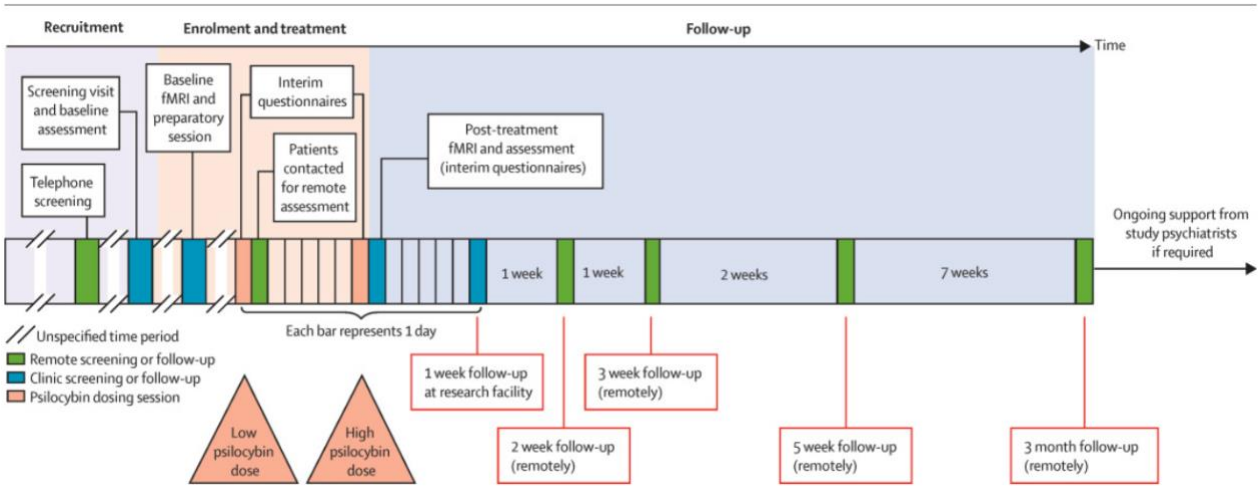

Figure 2. Timeline of feasibility study showing baseline setup, intervention, and follow ups before and after intervention [15].

Fig 2 shows the timeline of the pilot study. There is a screening process to select participants who are then given a preparatory session with a therapist. Participants are given the low 10 mg dose and followed up with every day for a week before receiving the higher 25 mg dose. After both doses have been administered, a follow up fMRI and QIDS-SR16 is taken. There will continue to be follow up periodically for 3 months [15]. This study differs from Roseman et al. study because there is also fMRI imaging of the brain before and after the dose of psilocybin [15].

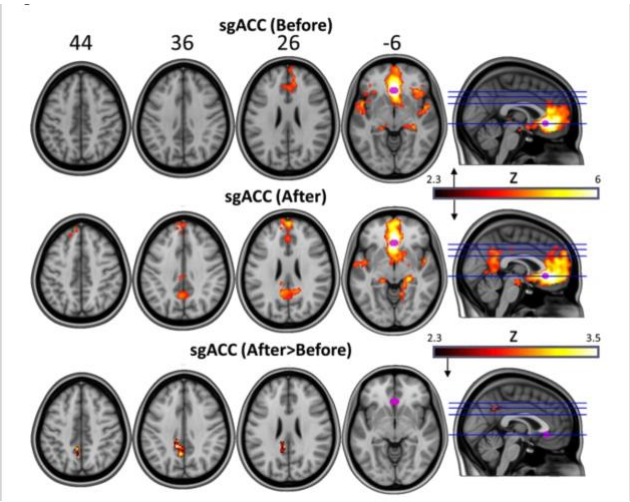

Figure 3. The Subgenual anterior cingulate cortex (sgACC) before and after the dosing of psilocybin [15].

Fig 3 shows that there was more resting state functional connectivity (RSFC) in the subgenual anterior cingulate cortex (sgACC) after receiving treatment [15]. The sgACC has clinical importance in the regulation of mood and has been proven to alleviate depression symptoms with deep brain stimulation [20]. The treatment in imaging showed that there was a "rapid and sustained antidepressant" effect from the psilocybin dosage [15].

Another controlled clinical study injected 75 µg of lysergic acid diethylamide (LSD) and a saline placebo two weeks apart. Participants were monitored and their mental state was measured using the Altered States of Consciousness (ASC) questionnaire and the Psychotomimetic States Inventory (PSI) at a baseline and two weeks after each dose. The results showed an elevated mood, but also showed high scores on the PSI, indicating a "psychosis-like" state [21]. These results were only observed after the LSD dose and not the saline dose.

A population study from 2001 through 2004 looking at general psychedelic usage concluded that psychedelics were non-addictive and did not cause brain damage over time. The same study noted lower rates of mental health issues in cases of psychedelic use [22].

Another population study from 2008 through 2012 concluded significantly lower rate of mental health issues in psychedelic users who had lower rates of past year suicidal thinking, planning, or attempts. The study attributed these lower suicide related rates to the use of psychedelics [23].

III. Gaps in Research

While all the mentioned studies boast promising results in decreasing depression symptoms for sustained periods of time, there are major gaps in the research. The studies mentioned before are all pilot studies and have not gone further than the initial testing.

Along with the slow progress of research, psilocybin is also illegal in the Unites States, making it hard to test in participants [24]. Despite being a Schedule I controlled substance, John's Hopkins was granted an NIH grant to investigate psychedelic effect on tobacco use [24, 25]. John's Hopkins now researches psychedelic use in depression, Alzheimer's, obsessive compulsive disorder (OCD), post-traumatic stress disorder (PTSD), anorexia, and alcohol abuse [26].

John's Hopkins has had many studies where the baseline GRID-Hamilton Depression Rating Scale values decreased, indicting less severe depression symptoms. The study also tracked any outside psilocybin use after the study and found none of the participants had any besides the 2 doses from the study and there were no long-term effects from the initial psilocybin use [27].

John's Hopkins' funding allows for them to freely explore the benefits of psilocybin when treating mental health issues, but otherwise the field of research is still restrictive and needs far more study.

IV. Conclusion

Many pilot studies have been done to test the effectiveness of psilocybin as a treatment for Major Depressive Disorder. All the aforementioned studies found statistically significant differences in MDD testing scores to warrant further investigation into psilocybin as a treatment

for MDD. Psilocybin has been shown to work effectively over extended period of time, with relatively low risks to those who ingest it.

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