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An Evaluation of Traditional and Non-Traditional Psychopharmacological Treatments for Major  
Depression

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## Abstract

Depression is one of the most prevalent mental illnesses within society today, with overarching effects in the social, personal, and professional lives of millions of individuals who are suffering. The typical treatment for major depression is often a prescription of an antidepressant, either exclusively or combined with another form of treatment, such as psychotherapy. The intended effect is to increase levels of neurotransmitters such as serotonin and dopamine within the brain to regulate mood and emotion. While this treatment is effective for some patients, not all find relief. Exploring and extending research into other substances that effect the 5-hydroxytryptamine (5-HT) and dopamine systems, such as psychedelics and cannabinoids, may reveal new ways to alleviate patient's depressive symptoms. In a regulated, controlled, and supervised setting, the use of substances such as LSD, psilocybin, and marijuana could expand the efficacy and impact of depression treatment for patients who have found limited relief or developed treatment resistance to traditional antidepressants.

Approximately 13% of the general population suffers from Major Depressive Disorder, which is characterized by symptoms such as depressed mood, loss of interest in once pleasurable activities, change in appetite or sleeping patterns, fatigue, and feelings of worthlessness (Centers for Disease Control and Prevention, 2013). These symptoms can often affect individuals' lives, both personal and professional. The prevalence of this mental illness has prompted research into the causes and possible treatments. Biologically, depression appears to be associated with changes in the 5-hydroxytryptamine (5-HT/serotonin) neurotransmitter system that results in lower levels of serotonin, which has effects on mood, emotion, and cognition (Ioannidis, 2008). To adjust these abnormal levels of neurotransmitters, several drug classes have been developed to target and increase the transmission of serotonin. Such drug classes include select serotonin reuptake inhibitors (SSRIs), monoamine oxidase inhibitors (MAOIs), and tricyclic antidepressants (TCAs). While such pharmacological treatments have improved symptoms in some patients, others have found little relief with such conventional methods, which leads to questionable levels of efficacy (Ioannidis, 2008). In the search for more effective treatments, some researchers and patients have begun turning their attention to alternative options.

The standard method that physicians and psychiatrists use to treat depressive symptoms are antidepressants such as MAOIs, tricyclics, and SSRIs. MAOIs are the oldest, often referred to as the first-generation antidepressants. Their mechanism of action involves blocking the enzyme monoamine oxidase, (MAO), that breaks down monoamines such as serotonin. This results in higher levels of monoamines, which is believed to improve mood regulation and emotional states. Tricyclic antidepressants were developed next, and have a mechanism of action that works by inhibiting the reuptake of biogenic amines, specifically norepinephrine and serotonin. SSRIs specifically target the reuptake of serotonin, which increases the amount within

the synapse (Ioannidis, 2008). Prescribing these drugs is often the first and most typical treatment modality prescribed by healthcare providers. Yet fewer than 50% of patients fully remit after antidepressant treatment (Trivedi, Nieuwsma, Williams, & Baker, 2009). In some cases, patients are prescribed different antidepressants, experience a change in dose, or add additional treatment such as psychotherapy. Still some patients remain treatment-resistant and struggle to deal with their symptoms or side effects experienced while on some antidepressant medications, such as headaches or nausea. Some side effects are more serious, such as suicidal thoughts or hallucinations, which can prove to be more harmful than the depression itself (Trivedi, Nieuwsma, Williams, & Baker, 2009). The struggle to isolate effective treatments for depression has led many researchers to look beyond conventional pharmacotherapy and into more experimental treatments, such as the use of psychedelics or cannabinoids, to help those who continue to suffer.

A psychedelic refers to a drug that can produce hallucinations and apparent expansion of consciousness. Some of the most well-known psychedelics are lysergic acid diethylamide (LSD) and psilocybin, which are currently categorized by the Drug Enforcement Administration (DEA), as a Schedule I drugs and are illegal for any purpose (Passie, Halpern, Stichtenoth, Emrich & Hintze, 2008). LSD is a semisynthetic derivative of an alkaloid found in ergot fungus, known as lysergic acid moiety. Psilocybin is a compound found naturally in mushrooms in the genus *Psilocybe*. Throughout the 1950s, psychedelics were used in experiments to induce “model psychosis” and to enhance psychotherapeutic treatments on a range of patients, including alcoholics and those suffering from personality disorders. Clinical trials continued by large pharmaceutical companies such as Sandoz, until the mid-1960s (Passie, Halpern, Stichtenoth, Emrich & Hintze, 2008). By that time, government protests had begun as psychedelics like LSD

were gaining popularity as recreational drugs. Research funds became limited as government protests began and experimentation dramatically dropped by the late 1970s.

Pharmacologically, psychedelics have various effects. They work primarily on the brain's 5-HT system and alter the transmission of serotonin in different regions. The primary receptor that psychedelic substances act upon is the 5-HT<sub>2A</sub> autoreceptor (Griffiths et al., 2016).

Substances such as LSD and psilocybin act as agonists at the 5-HT<sub>2A</sub> receptor, which has strongly been correlated with hallucinogenic effects, altering perception, cognition, and emotion (Passie, Halpern, Stichtenoth, Emrich & Hintze, 2008). When binding to the 5-HT<sub>2A</sub> receptor, psychedelics are inhibiting the inhibitory receptor, resulting in an overall increase of serotonin. Psilocybin administration has also been shown to decrease activity within the amygdala, which has a strong correlation with emotional responses (Kraehenmann et al 2015). While the exact neural mechanisms of this effect are not well-known, the ability to induce positive mood changes supports the potential of psilocybin and other psychedelics in their ability to work as antidepressants in more widespread ways than traditional antidepressants.

With such effects on serotonin levels, psychedelics have been a targeted antidepressant in many animal studies. A study conducted in 2014 used LSD to combat depressive-like behavior in rats (Buchborn, Schroder, Holtt, & Grecksch, 2014). The researchers performed a bilateral dissection of the rat's olfactory bulbs, which resulted in behavioral disturbances such as stress-associated locomotor agitation and avoidance learning. In human subjects, these symptoms can be associated with the agitation and emotional biases observed in some clinically depressed patients (Buchborn, Schroder, Holtt, & Grecksch, 2014). Following the bulbectomy, LSD was subcutaneously administered once every 24 hours for 11 days at a dosage of 0.13mg/kg. The same procedure was conducted with sham rats as a control, and with another group of rats who

had the bulbectomy, but were injected with saline. During this time, the rats were assessed by a pole-jumping test, where they had to learn to avoid electrical stimulation of their feet by jumping onto a pole. Each day their time was recorded. Initially, the bulbectomized rats performed at levels similar to the saline injected rats, while the sham rats performed the best. However, the bulbectomized rats receiving LSD began to improve over the course of a couple of days, and by the end of the 11 days, their responses had normalized to the level of the sham rats, while significantly differing from the saline rats (Buchborn, Schroder, Holtt, & Grecksch, 2014). Overall, the researchers were able to conclude that the LSD treatment was able to decrease avoidance learning, which has been proposed to model decreases in emotional stress.

Another psychedelic substance, psilocybin, also shows promise in being used as an antidepressant. A recent study was conducted specifically on cancer patients who show symptoms of depression and/or anxiety (Griffiths et al., 2016). This double-blind study assigned patients into one of two groups who received two doses of psilocybin. One group received a high dose (22 or 30mg/70kg) at their first session and a low dose at their second session (1 or 3mg/70kg) five weeks later. Prior to the psilocybin administration sessions, baseline measurements of depression and anxiety were taken by clinicians using the Hamilton Depression Rating Scale (GRID-HAMD) and the Hamilton Anxiety Rating Scale (HAM-A). Patients were also assessed at a six-month follow-up session. Results of the assessments showed that after the first session of psilocybin administration, 92% of high-dose participants showed a decrease in depressive symptoms. Low dose patients showed a 32% decrease in symptoms. Patients were also able to report their subjective ratings of anxiety, depression, and mood disturbance, all of which decreased after psilocybin administration. Clinician and self-reports of quality of life,

meaning, death acceptance, and optimism increased and were sustained at six months for 78% of patients experiencing depressive symptoms (Griffiths et al., 2016).

Another study targeted antidepressant resistant depressive patients who had failed to see a relief in symptoms after at least two courses of antidepressants (Carhart-Harris et al. 2016). Each patient was diagnosed with moderate-severe major depression. Psilocybin was administered orally in two sessions, the first dosage containing 10mg and the second containing 25mg, with a 7-day gap between sessions. Measurements of depressive symptoms were measured using the HAM-D and the Beck Depression Inventory (BDI) before administrative testing, 7 days after treatment, and three months afterward. All patients showed a decrease in depressive symptoms after 1 week, and 58% achieved remission after three months (Carhart-Harris et al. 2016).

Another path for future nontraditional antidepressant treatment is the use of cannabinoids. One of the major components of these substances is tetrahydrocannabinol, (THC), the active ingredient in *Cannabis*, which is more commonly known as marijuana. Drugs that contain THC, like marijuana, have been shown to affect several neurotransmitter systems in the brain, including the 5-HT and dopamine, (DA) systems. These systems, being linked to mood regulation and feelings of pleasure and reward, are often targeted for antidepressant treatment. The human body contains its own endocannabinoid system that is involved in emotional, cognitive, and motivational processes. Within the central nervous system, the presynaptic cannabinoid type 1, (CB1), receptors, are found in areas such as the cerebellum, basal ganglia, hypothalamus, hippocampus, medulla, and areas of the cerebral cortex (Valdez, 2017). The widespread locations and functional areas of these receptors that are activated by endogenous and synthetic cannabinoids allow for many complex effects to take place that alter behavior and neurochemistry. By better understanding these receptor pathways and the effects that certain



drugs can have on them, research may gain insight into developing more directed and efficient ways of altering the activity of these receptors to benefit those suffering from psychological disorders.

In one rodent based study, the focused cannabinoid used was cannabidiol, (CBD), which lacks the psychoactive ingredient of THC (Breuer et al, 2016). In this study, mice were injected with fluorinated CBD solutions and then subjected to a number of behavioral tests, most notably the forced swim test (FST). Those mice who received the CBD injections, specifically in a concentration of 3mg/kg, spent less time immobile in the forced swim test when compared to control mice. Immobility has been proposed to model a depressive-like state. These findings are promising for the more widespread use of CBD, as it can already be purchased in variety of forms in stores today, including oils and gummies. Higher doses of medical grade CBD has also been to prevent seizures in epileptics, which has shown promise in a growing number of people (Project CBD, 2018).

The CB1 receptor has been shown to be an important receptor in the potential regulation of certain depression symptoms. A lack of CB1 signaling has been shown to produce symptoms that mimic major depression (Gorzalka and Hill, 2011). In contrast, the activation of CB1 signaling has been shown to mimic the behavioral and emotional effects of many common antidepressants. In one study, researchers investigated these relationships further in mice by inducing depression-like symptoms with corticosterone, (CORT), and then using a combination of curcumin, (CUR), and dexamabinol, (HU-211), a synthetic cannabinoid, to counteract the depressive effects (He et al, 2017). CUR and dexamabinol both have been shown to have anti-inflammatory, antioxidant, and neuroprotective effects. Specifically, this study tested the ability of a Cur/HU-211 mixture to protect CB1 receptors from the effects of CORT. After analyzing

pre-condition levels of both DA and 5-HT, the mice were split into three groups, one which would receive injections of the Cur/HU-211 and CORT, one group that would receive only CORT, and one which would remain as a control with no injection. Behavioral changes were observed in the mice using the FST and brain neurotransmitter tests specifically analyzing DA and 5-HT levels. Levels of CB1 mRNA and proteins were also collected to gauge the health of the CB1 receptors. The findings were encouraging. The mice that were treated with the Cur/HU-211 decreased immobility time when compared than the mice only treated with CORT, who continued to express depression-like behaviors. In the measurement of neurotransmitter levels, the Cur/HU-211 induced more DA and 5-HT specifically in the hippocampus and striatum, surpassing the levels of the CORT and control groups. CB1mRNA expression levels were also analyzed, and it was found that these levels were highest again in the hippocampus and striatum of the Cur/HU-211 group and decreased in the CORT group (He et al, 2017). Collectively, it appeared that in a corticosterone induced depression model, a combination of curcumin and dexamabinol, a synthetic cannabinoid, was able to reduce depressive-like behavior and alter the neurochemicals of mice in a way that could be a future target for human research.

Another study analyzed depressive-like behavior and the cannabinoid system by using a social isolation stress model (SIS), which has been shown to induce depressive-like behaviors in rodents (Haj-Mirzaian et al 2017). The researchers used this model to observe the effects of depressive-like behavior in response to certain cannabinoid agonists and antagonists. One chemical compound, WIN55, 212-2 was used as a nonspecific cannabinoid agonist, and AM-251 was used as CB1 antagonist. Both were administered as injections, and each mouse was used once in each test condition. To establish pre-injection conditions, a group of mice were held in the social condition (SC) in a tank with six other mice, and another group were held in the

isolation condition (IC), with minimal experimenter interaction. The mice were then separated into a group of saline injections, a group of WIN55-212,2 injections, and a group of AM-251 injections. After administration, behavioral observation began. A FST and splash test, which involved an initial splash of a sucrose solution and sequential observation of grooming behavior, were conducted and used as measurements of depressive, motivational, and self-care behaviors. The results showed that the mice in the IC significantly increased immobility in the FST and decreased grooming behavior in the splash test, supporting its use as a depression inducing model. The use of WIN55, 212-2 at 3 and 5mg/kg decreased immobility time in the FST and increased grooming time in the splash test of IC mice. These effects were not observed in the SC mice. The mice who were administered the AM-251 increased immobility time and decreased grooming time in comparison to IC mice injected with saline. To add another level of analysis, researchers administered a number of injections in a sequential manner, with first an injection of WIN55, 212-2 one hour before the behavioral tests, and then an injection of AM-251 30 minutes before the tests. The results of this condition showed that AM-251 reversed the effects of WIN55, 212-2, with the same trends of increased immobility and decreased grooming time that were observed when only AM-251 was administered in IC mice. Overall, the results suggested that the administration of the cannabinoid agonist, WIN55, 212-2, reversed the depressive behaviors induced by IC while the administration of CB1 antagonist, AM-251 resulted in depressive-like behaviors and reversed the effects of WIN55, 212-2 (Haj-Mirzaian et al 2017). These relationships between agonists and antagonists observed in a social isolation model in mice provides insight into how such neurochemical relationships may be affected by possible drug therapies to combat depression symptoms in humans who may also find themselves in more socially isolated conditions.

Although there is a growing base of evidence for the benefits of psychedelics and cannabinoids as treatments for depression, approval and accepted medical use will be difficult to achieve. Certainly, additional research is needed concerning psychedelic and cannabinoid use in relation to depressive symptoms. Research with animal models have produced promising results, particularly within rodents, but human studies are rarer. However, there is gaining popularity in exploring the possible use of these substances, particularly cannabinoids, as treatments for multiple health problems, including pain management and anti-nausea medications for those undergoing cancer treatment (Williamson and Evans, 2000). Although not directly studying the antidepressant effects of cannabinoids, these studies may offer additional insights into the physiology and possible behavioral responses observed when these drugs are utilized, which may act as a springboard for future research and acceptance in other areas. Furthermore, while medically promising, the past use of psychedelics and cannabinoids as recreational drugs often hold them back from being considered as serious medical options (Patra, 2016). Even after presenting the public with evidence of the beneficial use, the stigma of these substances as “street drugs” that are further associated with other risky behaviors, continues to prevail. However, it is important to differentiate medical from recreational use, and that the push to legalize substances such as LSD, psilocybin and synthetic cannabinoids would be for intended medical use in a public setting, and if necessary, supervised by healthcare professionals (Baumeister, Barnes, Giaroli & Tracy, 2014). In some cases, a slow integration of medical marijuana treatment is beginning to grow, and it is possible that future facilities offering psychedelic use might establish themselves in a similar way. These developments would likely be established by individual states, and even then, be limited in the population eligible for treatment.

According to the Centers for Disease Control and Prevention, depression is the most common type of mental illness in the United States, and antidepressant medications are among the most widely prescribed medications, with billions of dollars in sales each year (Ioannidis, 2008). Yet the effectiveness of common antidepressants reveals that while some individuals experience improvement in their condition, many remain unchanged or minimally influenced by typical pharmacological treatments. As mental health continues to become a growing health concern, research into other options for treatment should be assessed for potential benefits that may affect a wider population in a more comprehensive and effective way. Psychedelics and cannabinoids may prove to be the next generation of antidepressant treatment if public and social policy agree that the medical potential that these substances may offer in a controlled setting outweigh their past use as recreational drugs. A continuation of the research into the mechanisms that affect depression and the possible new horizons and clinical trials of treatment options such as psychedelics and cannabinoids on their own and in accordance with other therapies may bring society closer to combatting the extensive symptoms of depression that affect millions of people worldwide.

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