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The Role of Psychedelics in Managing Anxiety, Depression, and Flashbacks of Individuals with Post-Traumatic Stress Disorder

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ABSTRACT

Background: The impact of psychedelic treatment on patients with posttraumatic stress disorder (PTSD) has become more intriguing to the psychiatric field. Because of the stigma surrounding illicit drug use, the scientific communities were unable to conduct thorough studies regarding the effects of psychedelics on the brain. These drugs could help many people with mental illnesses that have not found adequate success with typical treatments. In recent years, there have been studies conducted to examine the use of psychedelics for the treatment of psychiatric disorders such as PTSD. **Purpose:** The purpose of this review was to bring awareness to the effectiveness of long-forbidden psychedelic treatments such as psilocybin. **Method:** Using a review of scholarly articles, this paper examines the effects of psilocybin on anxiety, depression, and flashbacks in patients with PTSD. **Findings:** Findings indicate a therapeutic effect on patients with PTSD when using psilocybin. **Conclusion**: Based on these findings, the medical community should take steps toward novelty treatments for psychiatric diagnoses; however, further studies may be implicated. Stigma against this class of medications remains an issue.

INTRODUCTION

PTSD is a mental health condition that includes a hyperactive amygdala (process fear), hypoactive prefrontal cortex (logic), and hippocampus (long-term storage). This is caused by experiencing, witnessing, hearing it happen to a close friend/family member, or experiencing repeated traumatic events [1]. Individuals with PTSD suffer from depression, anxiety, and flashbacks which affect activities of daily living (see Figure 1). Multidisciplinary Association for Psychedelic Studies (MAPS) has been exploring the medicinal use of psychedelics since 1986. In 2018, MAPS achieved the Food and Drug Administration (FDA) approval for phase three trials for 3,4-Methylenedioxymethamphetamine (MDMA), breakthrough therapy, in the treatment of PTSD [2]. The purpose of this review was to uncover how and in what ways can psychedelics help those with PTSD.

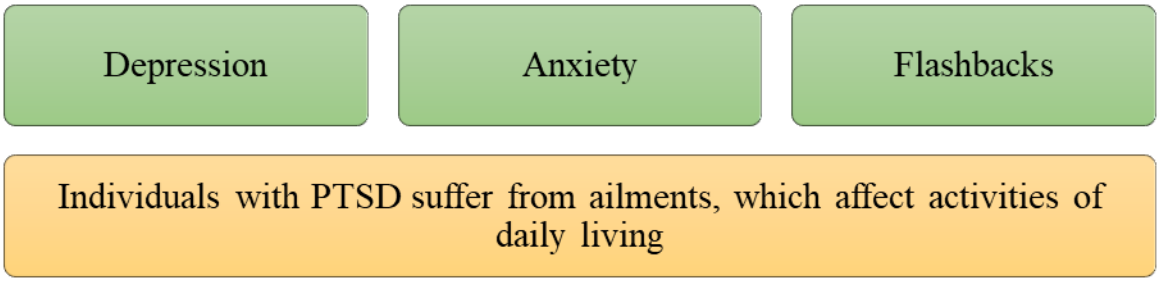

Figure No. 1: Individuals with PTSD suffer from depression, anxiety, and flashbacks

Background

Psychedelics, also known as hallucinogens, are a class of psychoactive substances thought to expand consciousness. These drugs include MDMA and LSD. These drugs were studied extensively between 1943 and 1970 for treating mental health disorders and addiction [3]. The research was halted in the 1970s with the enactment of the controlled substances act. As the field of psychedelic-assisted therapy develops, nurses can play a role in the research of these substances, which may soon be widely used in mental health disorders [3]. Psychedelics are a hallucinogenic class of psychoactive drugs with the primary effect of activating non-ordinary states of consciousness [4]. Emerging evidence from randomized, double-blind, placebo-controlled clinical trials suggests psychedelic compounds such as 3,4-methylenedioxymethamphetamine (MDMA), psilocybin, and lysergic acid diethylamide (LSD),

when administered as an adjunct to psychotherapy, that is, psychedelic-assisted psychotherapy (PAP), may be beneficial for treating substance use disorders, PTSD, depression, anxiety, and other psychiatric conditions [5].

METHOD

This was a review of existing literature. The information regarding the effects that psychedelics have on managing anxiety in individuals with PTSD is sourced from John Hopkins' Journal of Palliative Medicine, Frontiers in Psychiatry, and Taylor and Francis' Journal of Psychoactive Drugs and World Journal of Biological Psychiatry using the keywords PTSD and anxiety. Because the effects of psychedelics are a relatively new idea in Western medicine compared to current medication options for anxiety and PTSD, all sources used to gather data were found through Google Scholar or the university's online library.

The articles that were studied related to PTSD and depression came from scholarly sources including Taylor and Francis Online, ProQuest, and the Oxford International Journal of Neuropsychopharmacology. The purpose of these studies was to examine the effects of psychedelics on patients with PTSD, specifically regarding the co-occurrence of depression. The literature examined a multitude of previous experiments, while also conducting studies of their own to find more conclusive results. The research articles made a point to outline areas where further studies may be implicated.

Notable sources reviewing flashbacks related to PTSD were retrieved from scholarly sources such as Wiley's online library, natural medicine, and SAGE journals using keywords psychedelic therapy and flashback. The purpose of these studies was to examine the effects of psychedelic therapy on people who have PTSD flashbacks. Study reviews range from 2019 to 2021, beginning with one scholarly article about the history of MDMA and the psychedelic prohibition. Some studies used a variety of psychedelics, and some studied the effects of just one. Limitations, alternatives, and successes are discussed throughout each article on psychedelics.

FINDINGS

The findings are categorized into three major areas. The areas are anxiety with PTSD, depression with PTSD, and flashbacks in PTSD. Some pertinent drugs for treatment are mentioned. Gaps in the literature and the need for further studies are also highlighted.

Individual Suffering Anxiety and PTSD

Bandelow *et al.* [6] point out that 66% of individuals with PTSD also experience anxiety due to the prevalence of these illnesses in trauma-related populations. PTSD and anxiety share common ground in worrying. With PTSD, worrying is usually contained to the specific traumatic event, while anxiety is oftentimes worrying about the future. However, when both coexist at the same time in an individual, PTSD symptoms are exacerbated by anxiety, causing panic attacks, social anxiety, and specific phobias [6]. People with anxiety disorder are also more likely to experience PTSD symptoms after being exposed to a traumatic event than neurotypical people. PTSD used to be classified as an anxiety disorder but is now classified as a trauma and stressor-related disorder [6].

The struggles of a patient with anxiety and PTSD generally do not manifest in physical appearance. The patient may present neurotypical at first glance but might not be able to maintain eye contact; they may have trouble sleeping, have trouble focusing, and be easily distracted in addition to the defining characteristic of PTSD being flashbacks (see Figure 2). Patients with PTSD and anxiety will also be more socially withdrawn than patients without anxiety [6].

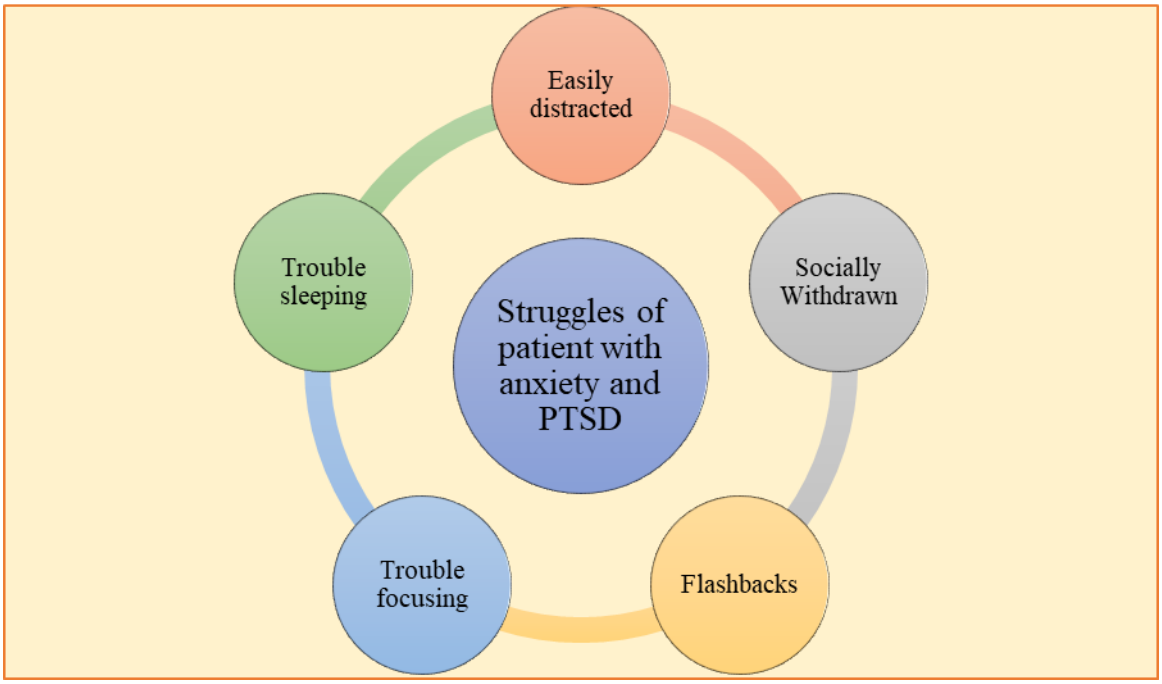

Figure No. 2: Struggles of the patient with anxiety and PTSD

Bandelow *et al.* [6] explain that the difference between someone experiencing the normal human emotion of anxiety and the levels of anxiety experienced in PTSD is linked to environmental and biological factors. Environmental factors are usually from traumatic events that occurred during a person's childhood upbringing, but that does not mean an individual cannot develop PTSD as an adult. Biological factors impact anxiety in PTSD because specific fears and phobias can be passed down, making certain people predisposed to these coexisting disorders [6].

PTSD and anxiety heavily impact the way an individual lives out their daily life compared to someone without mental illness. For example, a neurotypical person might drive themself to work every day with no issues, but someone with PTSD and anxiety might have a hard time deciding what route to take to work because of different possible outcomes, and they might fear getting into a car accident due to past traumas or general feelings of anxiety.

Individual Suffering Depression and PTSD

Some of the key features of PTSD are the recurrence of depressive and negative feelings or thoughts regarding oneself and the presence of suicidal ideation [7]. Patients who are diagnosed with PTSD and the comorbidity of depression may exhibit disruption in personal hygiene, loss of

appetite, isolation, and numb effect (see Figure 3). It is important to note that depression is one of the classic comorbidities that come along with this condition. Approximately 50% of patients diagnosed with PTSD also present with the major depressive disorder [7]. However, current medical treatments have not been proven to have as great of an impact on mental health conditions as was hoped. For example, the use of selective serotonin reuptake inhibitors (SSRIs) in the treatment of depression has only been shown to have effects on 60% of users, and only 20-30% achieve remission long term. In one-third of patients using traditional antidepressants, treatment-resistant depression occurs, which poses a challenge for physicians who are trying to help their clients achieve acceptable mental health statuses [7].

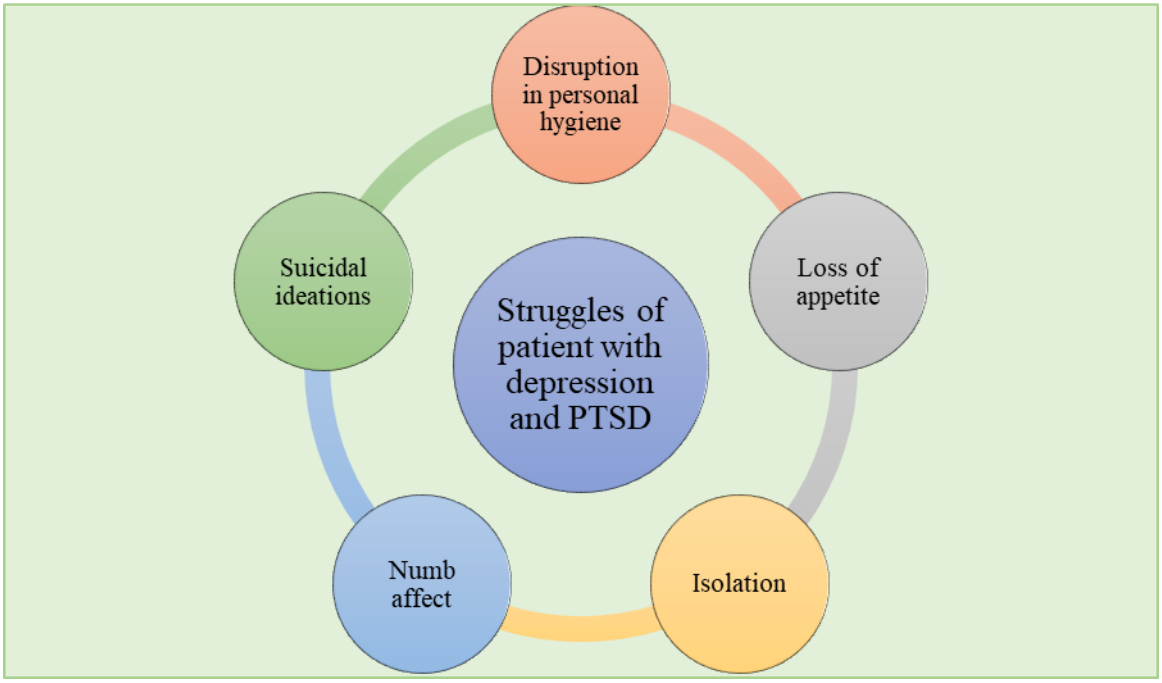

Figure No. 3: Struggles of the patient with depression and PTSD

There have been no major developments in the treatment of depression since the 1980s when SSRIs were approved for clinical use, and the demand for new advancements in medical interventions has been on the rise [7]. Doctors are now seeking new options to better the overall care of their patients with depression and have looked to psychedelics as a possible option. The use of these alternative therapies was studied before the 1950s, and over 1,000 papers were published containing the results of psychoactive treatment on thousands of patients [7]. New research has the potential to uncover more therapeutic interventions for patients struggling with

PTSD and may assist in reducing the symptoms of depression. So, the question is as follows: How effective is psilocybin on the management of depression in patients with PTSD?

The occurrence of depression in patients with PTSD is about 50%, which indicates a need for antidepressant management during severe symptomatic periods [7]. Depression is a difficult disease to treat by itself, and the presence of PTSD adds another layer of complexity in finding the right course of medications for everyone. The root of PTSD is attributed to a traumatic experience, followed by the inability to cope. Family history of depression or traumatic events has proven to be a link and increases the risk of developing major depressive disorder on top of PTSD.

A patient experiencing major depressive disorder may have abnormalities in the levels of neurotransmitters in the brain including serotonin, noradrenaline, and dopamine, which lead to an imbalance of emotional regulation [8]. Depression manifests as lack of energy, poor appetite control, irregular sleeping patterns, inability to focus, anhedonia, and poor medication adherence. These symptoms may inhibit the patient from living a normal life and have the potential to incapacitate someone's ability to care for themselves. It can lead to mandatory hospitalization or death by suicide. The use of psilocybin may enhance the quality of life of patients living with depression and PTSD [9].

Individual Suffering Flashbacks Symptoms in PTSD

Flashbacks are a dissociative reaction in which the individual feels or acts like they are thrown back into the traumatic event via thoughts, smells, visuals, and noises [1]. Symptoms are individualized and range in severity depending on a multitude of factors. As seen in Figure 4, some common symptoms of PTSD related to flashbacks are nightmares, night terrors, hallucinations, intrusive thoughts/memories, and reenactments of the event(s) [1].

Behaviors of patients living with flashback symptoms of PTSD are complex and varied. Some claim to experience one or less a week while others experience more than ten flashbacks per day. Another factor is the intensity of the flashback. No matter where on the spectrum the patient falls, some common behaviors of patients living with PTSD flashbacks are disconnection from reality, mood swings, and isolation [10].

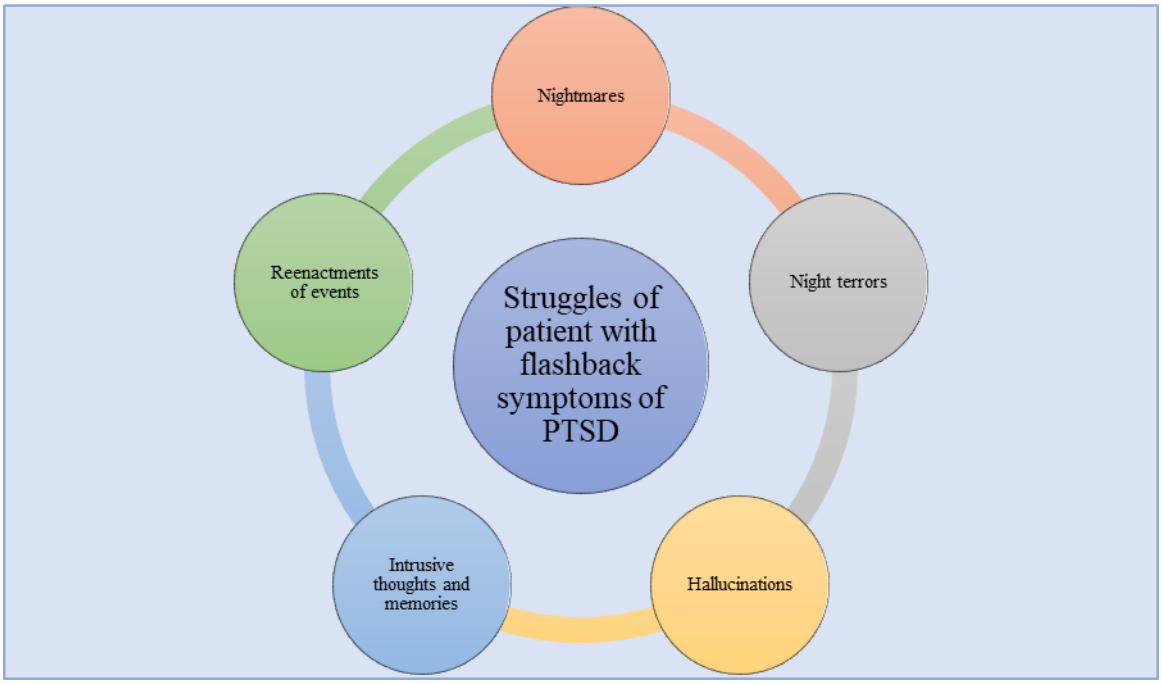

Figure No. 4: Struggles of the patient with flashback symptoms of PTSD

The origins of MDMA are not well known due to the common myth that this drug was patented as an appetite suppressor in 1912 [11]. Rather, the drug was being studied as a precursor in the new synthesis of hemostatic substances. As shown in Figure 5, the German pharmaceutical company Merck studied the effects of MDMA from 1927-1959 and began the first human studies in 1960, soon after the researchers truly got a glance at the wonders of MDMA drug therapy [11]. The prohibition of psychedelics began in 1966 prohibiting LSD and DMT. By 1970, the United States expanded the list adding MDMA, psilocybin, psilocin, mescaline, peyote, and cannabis. These substances became Schedule 1 drugs soon after the war on drugs began in 1971 [12].

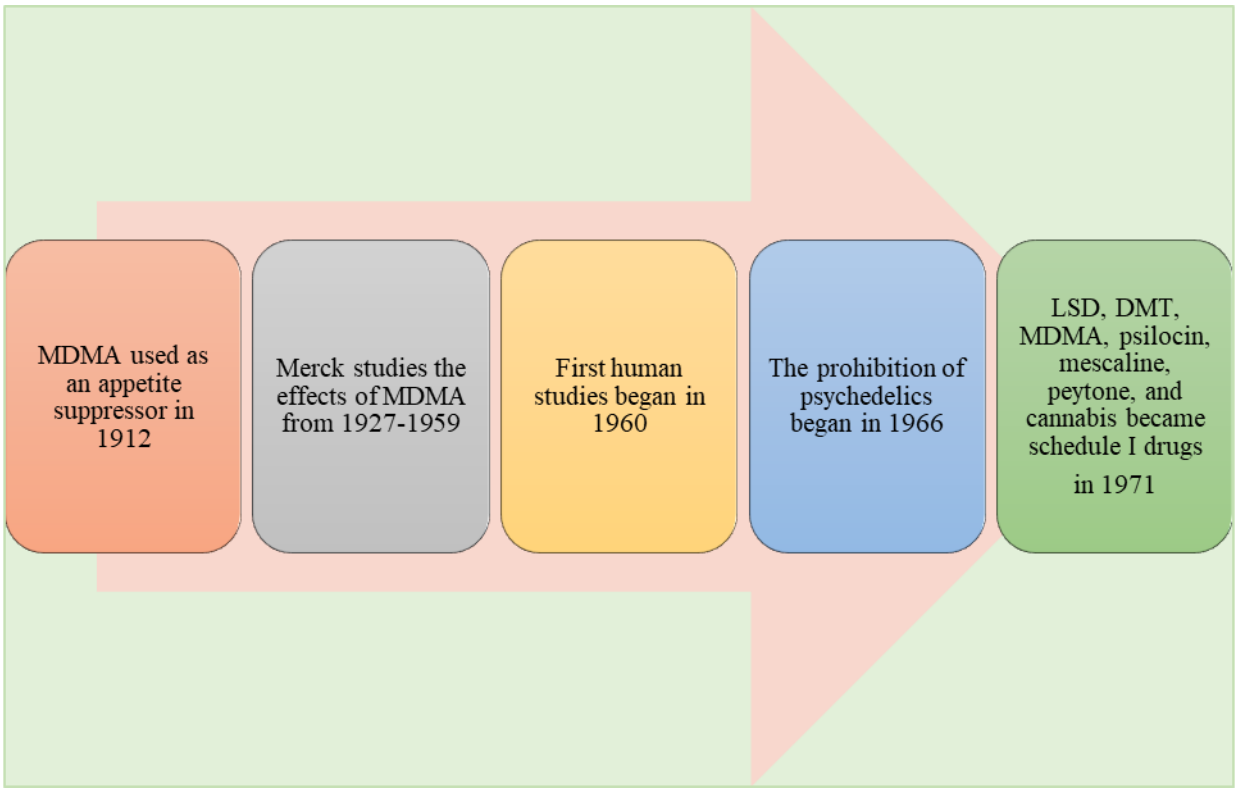

Figure No. 5: Origins of Psychedelics and Prohibition

In the 1990s the psychedelic renaissance began with psychiatrists and researchers coming together worldwide beginning with the study of DMT and LSD. Over the past thirty years, research has vastly expanded and is rapidly gaining traction. Notably, phase one and two randomized trials of MDMA-assisted psychotherapy treatment for PTSD flashbacks were conducted between 2004-2017 showing astonishing results [12]. Davis *et al.* [13] studied the effects of 5-Methoxy-N, N-Dimethyltryptamine (5-MeO-DMT) which is a plant species found notably in the Sonoran Desert/Colorado River toad. This psychoactive drug has improved PTSD flashback symptoms through mystical-type experiences, experiences of ego dissolution, and increased mindfulness-related capacities.

Psychedelics are a classification of compounds that stimulate emotional, cognitive, and physical effects upon an individual which helps provide a sense of openness of oneself. Krediet *et al.* [14] used MDMA, ketamine, and cannabis as well as classical psychedelics including psilocybin and LSD. Each drug was given in a calm and appropriate setting, optimal for patient healing. Psychoactive properties in psychedelic drugs catalyze the psychotherapeutic process through

increased neuroplasticity both emotionally and cognitively. Physiologically, the brain on psychoactive drugs has decreased fear and arousal (those from PTSD typically suffer from some degree of hypervigilance) which builds trust, extinguishes fear, and stores long-term memories [14]. These effects dissolve extreme effects of flashback symptoms of PTSD sufferers.

Treatment Options

So far highly promising preliminary data have been produced with psilocybin in anxiety, depression, smoking, alcoholism, and with MDMA for PTSD (PTSD) and alcoholism [15]. Serotonergic hallucinogen drugs, such as psilocybin, bind most potently as agonists at the 5HT2A receptor, producing profound changes in perception, mood, and cognition [16]. Some of these drugs have been or are currently being investigated in small Phase 2 studies for depression, alcoholism, smoking cessation, anxiety, and posttraumatic stress disorder [16].

Podrebarac *et al.* [17] conducted a randomized controlled trial exploring the therapeutic potential of psilocybin-assisted psychotherapy for alcohol dependence. Throughout the trial, many individuals have reported experiences that take a variety of forms, including spiritual insights, beatific visions, and communion with the Divine. Should psychedelic medicine continue to show treatment promise in clinical trial stages, there is a strong possibility that these medicines will become an integral part of psychotherapy, which will require integration of direct spiritual experiences and spiritual care into the healing process [17].

In a review of multiple studies, Berkovitch *et al.* [18] found a quick and important response after psychedelic administration that lasted for several months, even after a single dose. However, most of these studies were descriptive or open-label studies conducted on small samples. No severe adverse events occurred. Psychedelics are promising treatments for anxiety, depression, and addiction; their efficacy is quick and sustainable, and they are well tolerated. These effects need to be confirmed in larger studies and compared to standard care [18].

Begola and Schillerstorm [19] investigated the literature regarding the psychotherapeutic uses of hallucinogens in psychiatric disorders. The results showed that a variety of substances have been evaluated in the treatment of psychiatric disorders, including ayahuasca, ibogaine, ketamine, lysergic acid diethylamide, 3,4-methylenedioxymethamphetamine, and psilocybin. The

conditions treated ranged from depression to autism, with the largest volume of research dedicated to substance use disorders. Most studies that were reviewed demonstrated significant associations with improvement in the conditions investigated [19].

Reiff *et al.* [20] stated that the most significant database exists for MDMA and psilocybin, which have been designated by the U.S. Food and Drug Administration (FDA) as "breakthrough therapies" for PTSD and treatment-resistant depression, respectively. Randomized clinical trials support the efficacy of MDMA in the treatment of PTSD and psilocybin in the treatment of depression and cancer-related anxiety. The research to support the use of LSD and ayahuasca in the treatment of psychiatric disorders is preliminary, although promising. [20].

Current Studies on Psychedelics

Most studies that were reviewed demonstrated significant associations with improvement in the conditions investigated. However, it was difficult to draw definitive conclusions as most studies suffered from small sample sizes, inconsistent measures, and poor study design. To properly assess the risks and potential benefits of hallucinogens in psychiatric treatment, there is a need for well-designed, standardized studies that demonstrate the impact of hallucinogenic substances on psychiatric conditions [19]. Current research with medicinal psychedelics, usually as an adjunct to psychotherapy, has shown encouraging results in treating mood disorders [21]. However, there are challenges regarding blinding and sample sizes remain small, and there have been no definitive Phase III studies (aside from MDMA for PTSD). Further work exploring novel formulations, interface with pharmacogenomics and the microbiome, and inflammatory pathways can be advised [21].

Reiff *et al.* [20] state, overall, the database is insufficient for FDA approval of any psychedelic compound for routine clinical use in psychiatric disorders at this time, but continued research on the efficacy of psychedelics for the treatment of psychiatric disorders is warranted. Of the studies that are going on currently, the majority aim to investigate methylenedioxymethamphetamine (MDMA) (45.7%) and psilocybin (41.4%). Studies evaluating ayahuasca, lysergic acid diethylamide (LSD), ibogaine hydrochloride, salvia divinorum, 5-MeO-DMT, and DMT fumarate were less common at 1.4%, 4.2%, 2.8%, 1.4%, 1.4%, and 1.4% of total registered studies, respectively [4]. In a review of 13 studies, Basedow *et al.* [22] found that LSD,

ayahuasca, and peyote may have different neuropsychological consequences associated with their use. While LSD users showed reduced executive functioning and peyote users showed no differences across domains, there is some evidence that ayahuasca use is associated with increased executive functioning [22]. Figure 6 shows that currently MDMA and psilocybin are the most studied.

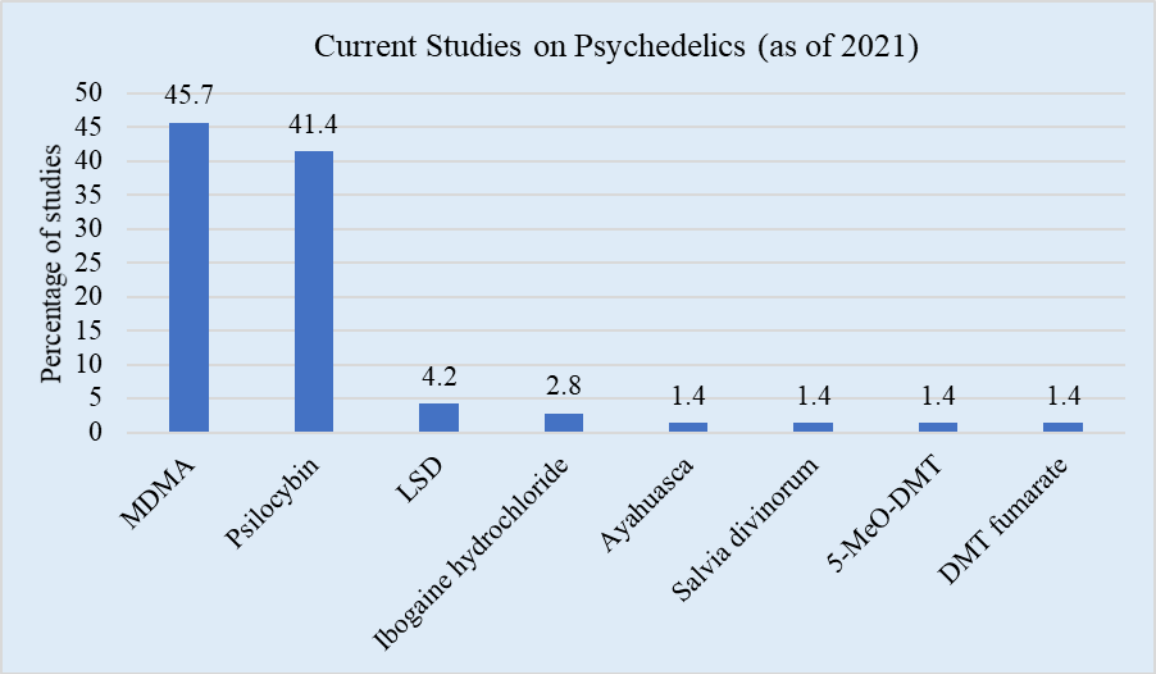

Figure No. 6: Current studies that are going on related to psychedelics

Summary of the Literature

Data from most of the studies reported positive outcomes with almost no data rejecting the hypothesis that psychedelics are an effective treatment for managing anxiety in patients with PTSD. Psychedelics pose no serious adverse effects and have low levels of tolerance noted from the studies [23]. Vargas *et al.* [24] pointed out that the use of psychedelics is quite groundbreaking because they focus on healing the pathological neural circuitry rather than masking disease symptoms like current medication used to treat anxiety and PTSD. However, even with positive outcomes present, it is still important that this treatment is given in therapeutic doses by trained providers in a safe environment [25].

The peer-reviewed articles outlining the effects of psilocybin on PTSD and depression have uncovered a new era of treatment regarding mental health conditions. The complexity of PTSD makes it difficult to treat with first-line drug therapies since these therapies only affect a few of the imbalanced neurotransmitters in the brain. Treatment-resistant depression, which occurs in over half of patients with PTSD, has shown the most promising results during clinical trials with psilocybin because they can manipulate multiple neurotransmitters with one chemical compound [9]. Research has also discovered that if administered in a controlled environment, psilocybin has long-lasting positive effects on the occurrence of depression [8]. In one study containing patients with major depressive disorder and cancer, researchers found that 92% of patients who were receiving high doses of psilocybin therapy saw a decrease in depressive symptoms after just five weeks, and 67% of patients achieved remission after a three-month follow-up [8]. The science behind the use of psilocybin has been reviewed and reestablished through more recent studies and requires more attention from the medical community in exploring the different benefits of this psychedelic [26].

Paroxetine and sertraline are the only current FDA-approved treatments, which have shown little improvement and effectiveness for individuals with PTSD symptoms including flashbacks [27]. Due to the complex nature of PTSD flashbacks, targeted neurotransmitter treatment is difficult and tedious. Some patients describe psychotherapies as emotionally taxing. This includes feelings of detachment, fragmentation, and decreased tolerance for stimuli. These factors and more are common reasons that lead to the incompletion of psychotherapy [27].

Special operations force veterans and combat veterans have shown to have an increased risk for severely debilitating PTSD. These risks include traumatic brain injury (TBI), exposure to hazardous chemicals, and other life-threatening injuries/toxins [13]. In the past, treatment for these veterans has been limited due to the complexity of the disorder as well as the common multitude of comorbidities that coincide with having been in the service. Recent studies of psychedelic therapies show potential for new treatment approaches for veterans. As shown in Figure 7, promising analysis of phase two MDMA studies has led researchers to push for phase three clinical trials which were finally approved in March of 2021 [28]. This observational study includes the use of three sessions of MDMA-assisted therapy. Participants will be measured

using the DSM-5 and CAPS-5 total severity score which are PTSD diagnostic measurements. The estimated completion of the study is in March of 2025 [28].

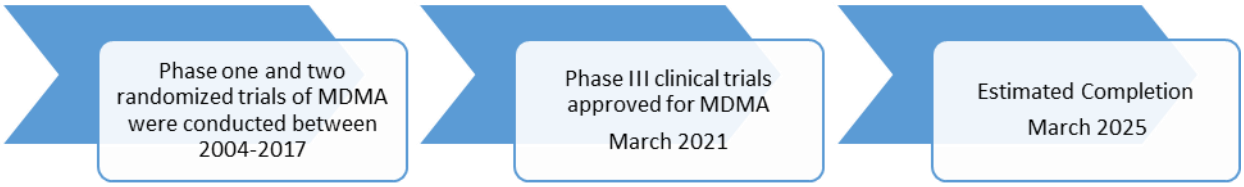

Figure No. 7: Three phases of clinical trials for MDMA

DISCUSSION

Studies support the use of psychedelics to manage anxiety related to PTSD. In a study conducted by Luoma *et al.* [23], evidence supported that 80% of people who participate in psychedelic-assisted therapy will have more beneficial outcomes than the individuals who received a placebo. Another study suggests that psychedelics impact brain function even after the drug is no longer in the body, as tested on rats [29]. Vargas *et al.* [24] discussed that PTSD and anxiety inflict chronic stress on the brain, resulting in the prolonged release of glucocorticoids which ultimately lead to atrophy of the hippocampus and prefrontal cortex. Taking psychedelics changes the neural circuitry causing an increase in cortical thickness and cerebral blood flow in the prefrontal cortex which can be attributed to improved moods and lessened anxiety [24]. Overall, the results from the studies were overwhelmingly positive, supporting the use of psychedelics for the treatment of managing anxiety in people with PTSD.

When caring for an individual who has anxiety and PTSD, the nurse must form a trusting relationship with the client. After the client builds trust and feels safe around the nurse, they are more likely to share their feelings surrounding their illness and may be more motivated to find treatment such as psychedelics if they have a trusted person with whom to discuss their options. If a patient decides to try psychedelic treatment options, there is a chance the patient will not need any more long-term interventions because of the long-lasting effects of the drug [29].

Psychotherapy is recommended regardless of treatment type. As Byock [25] stated, in reexamining the use of psychedelics in pharmaco-assisted therapy, we must not allow preconceptions, politics, or puritanism to prevent suffering people, who are now considered helpless and hopeless, from receiving promising, at times life-saving, treatments; it is unfair for anyone to take away what might be the only opportunity for someone's illness to improve because of the provider's personal beliefs. Outcomes can be evaluated by asking the client if their levels of anxiety have decreased, if they report fewer nightmares and if they notice being able to perform activities of daily living with more ease.

Based on clinical findings, the scientific community believes that there are many benefits related to the use of psilocybin in patients with PTSD and depression. It is the job of the medical community to constantly be reevaluating their methods of care and adapt to new evidence-based practice. The implementation of these newfound therapeutic agents could spark a plethora of new approaches to mental health. For example, if these drugs were legalized for use in psychiatric treatment, nurses could administer the medication as a controlled substance to ensure patient safety. They could then monitor the patient one-on-one to ensure nothing went wrong and perform interventions as they saw fit.

The nursing outcomes that are desired include reduction of depressive symptoms, refraining from self-harm or suicidal tendencies, increase in capability to care for themselves, and improved quality of life. Reducing depressive symptoms would assist the patient in having adequate mood regulation and could give them more motivation to pursue life-sustaining activities. Increasing the ability of the patient to care for themself is one of the main outcome goals, as that would qualify them for discharge from a psychiatric facility.

Krediet *et al.* [27] state that MDMA has shown a reduction in fear and shame with increased feelings of trust and safety. This increases the person's connection to others which helps them feel more comfortable reaching out when they need support during a trigger or flashback. Davis, *et al.* [13] explained how 5-MeO-DMT showed a strong reduction in flashbacks, cognitive impairment, depression, and anxiety in veterans during the program. Additionally, this program suggests that 5-MeO-DMT offers quick, vigorous, and well-tolerated treatment for a variety of psychiatric and cognitive symptoms. This is important to note as veterans are a vulnerable

population with high rates of addiction and suicide. Although this program shows a 79% overall improvement of PTSD flashback symptoms, more studies need to be conducted to establish efficacy and reliability in 5-MeO-DMT therapy [13]. Mithoefer *et al.* [12] analyzed six randomized, double-blind phase two studies that were in the United States, Switzerland, and Israel. Of participants in the active dose group, 54.2% no longer met PTSD diagnosis criteria for flashbacks compared to 22.6% of the control group. Although it looks as if MDMA shows promising relief of PTSD symptoms of flashbacks, experimental third sessions have shown even further clinical symptom reduction. From these results, ongoing phase three trials began in 2018 [12].

Mitchell *et al.* [28] evaluated participants over 18 weeks after receiving MDMA therapy. They did not have any safety issues in their randomized double-blind study which aimed to decipher the efficacy of MDMA-assisted therapy with placebo. There were 15 studies including two in Canada and two in Israel. The participants of these studies showed a significant reduction in the severity of PTSD flashback symptoms including decreased suicidal ideations, decreased occurrences of flashbacks, increased socialization, and more [28]. However, Mertens *et al.* [30] warn, the therapeutic mechanisms of classical psychedelics are currently unknown. Rubin-Kahana *et al.* [31] warned of a PTSD onset after a psychedelic experience. Healthcare providers who treat patients should be aware of these irregular presentations.

CONCLUSION

PTSD is a mental illness that manifests itself in the form of intense fear usually related to a specific traumatic event. Individuals with PTSD often suffer from anxiety, depression, and flashbacks which can make tasks of everyday living very difficult. Multiple studies have shown that the use of psychedelics in the treatment of PTSD is effective for lessening unpleasant symptoms of the disorder and healing neural pathways of the brain to provide long-lasting, sometimes permanent beneficial outcomes.

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