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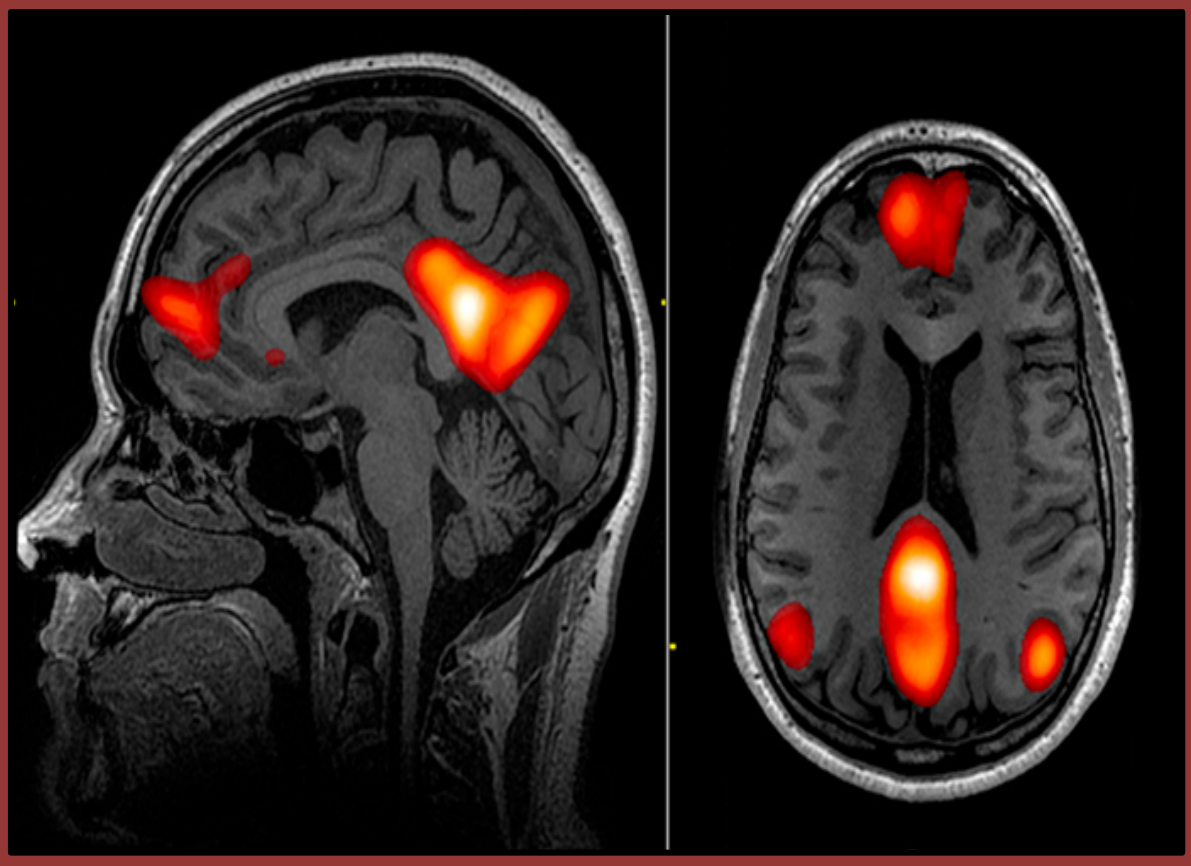

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- Ayahuasca and Treatment of Post-Traumatic Stress Disorder: A Case Report

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Welcome

Dear Reader,

As the co-founders of The Journal of Psychedelic Psychiatry, it is our honor and privilege to welcome you. We hope you will find this inaugural issue of the journal as educational, intellectually stimulating, and thought-provoking as the Editorial Board did during the compilation process. The Journal of Psychedelic Psychiatry was founded with the intent to collect and distribute high-quality research that utilizes psychedelics in the treatment of psychiatric disorders. It is our firm belief that psychedelics, when used appropriately in properly selected patients in psychotherapeutic environments, offer a potentially novel and revolutionary treatment for severe intractable psychiatric disorders. Psychedelics such as Ketamine, LSD, Psilocybin, and MDMA have showed renewed promise in the management of conditions ranging from treatment-resistant major depressive disorder, chronic post-traumatic stress disorder, tobacco use disorder, and alcohol use disorders just to name a few. The proposed mechanism of decreased activity within the Default Modal Network, which is postulated to be the part of the brain correlated with ego identity and some degree of consciousness, results in increased activity between otherwise weakly interconnected cortical areas. This finding alone has profound implications for future areas of study and while current efforts are ongoing more research will be needed to further investigate in an attempt to better understand and explain these processes.

Psychedelic research since the late 1970s has mainly been confined to academic institutions in small scale studies due to the negative cultural reputation that became attached to psychedelics after the broad-scale use during the 1960s which resulted in widespread concern and fear of psychedelics that was largely unfounded. These researchers who continued to investigate psychedelics despite this environment have earned our deepest respect. Without these individuals, the potential use of psychedelics for the treatment of severe psychiatric disorders might have been set back decades or even centuries if it was even considered at all. However, because of negative connotations associated with psychedelic use, the conclusions reached by these researchers has been dispersed across numerous fields of study from the basic science of psychedelic structure and function, to functional neuroimaging of the effects of psychedelics on the brain, and most recently the clinical implications of the treatment of severe psychiatric disorders. It is here that the Journal of Psychedelic Psychiatry seeks to establish a foothold. As the use of psychedelics for the treatment of psychiatric disorders becomes more prevalent the mistakes of the past must not be repeated insofar as they would lead to another decades-long delay in implementation of psychedelics as a treatment option. If psychedelics are as effective as we believe them to be based on the available evidence, it is of the utmost importance that the forthcoming studies are subjected to rigorous and critical analysis to ensure that psychedelics are used appropriately to maximize the benefits and mitigate against the potential risks. We feel that The Journal of Psychedelic Psychiatry is well-positioned to facilitate clinical psychiatrists, with limited or no knowledge about psychedelics, in this transition from the laboratory to the clinic. We hope that you will join us as we continue to provide educational information and clinical insight in this ever-changing and evolving landscape of psychedelic psychiatry.

Tyler Kjorvestad, M.D.
Gershom Hernandez, M.D.

Article

LSD: A Comprehensive Review

Gershom Hernandez, M.D.

Objective: This paper aims to compile the history, available data, pharmacology, notable studies, current neuroimaging studies, and psychology of Lysergic acid diethylamide (LSD) in order to assess any potential medical utility.

Methods: Literature Review

Discussion: While promising, notable studies do not provide significant evidence for clinical use. However, the evidence is compelling enough that more research and knowledge is warranted.

INTRODUCTION

Lysergic acid diethylamide (LSD), since its advent, has been a controversial substance and is currently considered to have no medical or therapeutic use. Despite being a schedule I controlled substance, there has remained interest in the use of LSD and other psychedelics culturally, recreationally, spiritually, and in combination therapy.

HISTORY

D-Lysergic acid diethylamide (LSD), a potent derivative of ergot alkaloids, was synthesized by Albert Hofmann in 1938 in Basel, Switzerland, at the Swiss pharmaceutical company Sandoz Laboratories. It was labeled LSD-25, as it was the twenty-fifth derivative that Hofmann had synthesized from Scilla glycosides. Ergot alkaloids, such as *Claviceps Pururea,* were notoriously thought to be responsible for episodes of mass poisoning in Medieval Europe. Ergotamine, another ergot, was used during childbirth due to vasoconstrictive and uteroconstrictive properties. Sandoz tasked Hofmann with synthesizing derivatives of ergot alkaloids in the hopes of finding some medical usage, which were thought to most likely resemble the medical applications of Ergotamine. Early animal testing found the compound unremarkable as it demonstrated no physiological effects. No further investigations were done for 5 years and Hofmann described a "peculiar presentiment" that led him to re-evaluate the molecule. Hofmann synthesized the chemical again in 1943 and on April 16th of that year, he accidently exposed himself to a small, unknown amount. He noticed unusual psychotropic effects of "restlessness", "intoxicated-like condition", and "kaleidoscopic play of colors". He reported the effects lasting approximately 2 hours. On April 19, 1943, he intentionally ingested 250mcg of LSD-25. Hofmann had meant this to be a conservative dose, thinking 250mcg miniscule as compared to other ergot alkaloids. That day, Hofmann noticed the acute effects of anxiety and intense perceptual disturbances and had an assistant escort him home by way of bicycle ride. As a result of these events, April 19th is known as "Bicycle day" culturally among LSD enthusiasts. When examined in his home by a doctor, he was reassured that nothing physiologically was amiss, apart from dilated pupils. Sandoz had increased interest and requested further investigation into LSD-25 after Hofmann's bicycle day. The compound was found to be physiologically nontoxic and very potent. In 1947 it was marketed as Delysid. At this time, it was readily available for interested parties wishing to study LSD, which was distributed from 1949 to 1966 for psychedelic research, with little to no restrictions, to researchers, psychiatrists, and psychotherapists for study[1].

In the early 1970's clinical research on LSD abruptly came to a halt, as LSD was deemed a controlled substance. In 1967, the United Nations Convention on Drugs made LSD a Schedule I controlled substance. As defined, any schedule I substance has no accepted medical use and the maximum potential for harm and dependence. Historically, this was influenced by political and cultural pressures concerning the drug[2]. During the 1960's, as the drug made its way into recreational usage, there was also an upheaval of tensions between cultural and authority figures, especially in the United States. Notable cultural figures significant to the psychedelic movement were Alan Waats, Timothy Leary, Ram Dass, and Ralph Metzner[3]. While the cultural impact of these notable figures, among others, is significant, this paper will focus primarily on the research aspect. Researchers contributed to the cultural and clinical knowledge of LSD and its potential benefits to alcoholism, depression, anxiety, terminal illness, tolerability, and side effects.

In 1950 Missouri, two researchers, Busch and Johnson, published one of the earliest studies of LSD using 21 patients. These patients were mainly hospitalized and diagnosed with Bipolar Disorder or Schizophrenia. They found that all 21 patients that were given LSD showed "increases in activity", concerning their illness. This was found to be more pronounced in manic patients. As a follow-up, the researchers provided 8 additional patients with LSD, 3 of whom had catatonic schizophrenia, 4 with "psychoneurosis" and 1 with "psychosomatic" disorder. The study was limited due to the ability to provide a control and subjective psychometric assessments, such as describing the effects of LSD as "disturbing the barrier of repression", "patients were able to re-evaluate the emotional meaning of some of their symptoms and improved". Two of the psychoneurotic patients "improved sufficiently to discontinue treatment"[4]. In a separate study in 1952, 59 patients, all with schizophrenia were given LSD or mescaline, administered with high variability. Seventeen had "pseudoneurotic" schizophrenia, twenty-six had "undeteriorated" schizophrenia, and sixteen had "deteriorated" schizophrenia. Those with deteriorated schizophrenia had "catatonic withdrawals" and there seemed to be no positive benefit to the other groups[5]. In 1953 and 1954, two studies were performed using LSD in patients with Schizophrenia and had similar results, with worsening in "deteriorated" schizophrenia, and possible improvement in "pseudoneurotic" forms being reported. Pseudoneurotic schizophrenia is no longer used as a clinical diagnosis but was considered a subgroup of patients with predominant anxiety symptoms which masked a latent schizophrenia[6]. Pan-anxiety, panneurosis, acting out behavior, and pansexuality were included in the definition[7]. Unfortunately, these definitions were not well defined. Pseudoneurotic schizophrenia was a diagnosis prior to the systematic and clinically applicable utility of the Diagnostic and Statistical Manual of Psychiatry (DSM). This illustrates the clinical limitations of early studies and the limited utility and negative effects that LSD has on patients with schizophrenia.

In the late 1950's and early 1960's studies with LSD administered to patients with Schizophrenia or mania gradually diminished. The fact that LSD worsened symptoms of psychosis led researchers to take a different approach, but interest in the potential for LSD to induce a psychotic state continued. In 1954, at Powick Mental Hospital in the United Kingdom, 36 patients with the diagnosis of "psychoneurotic" were treated with varying doses of LSD. Psychoneurotic symptoms were

defined as "between the borderline of psychosis and neurosis"[8]. Borderline was a term that originated in the 1800's and initially meant "between psychosis and neurosis", but that meaning had been lost by the early twentieth century as it became used to describe the "perceived unanalyzability of patients with psychosis versus those with neurotic illness"[9]. LSD dosage was initiated at 25mcg and increased until an adequate reaction occurred. Dosage varied but was predominantly given weekly and in combination with psychotherapy which was referred to in the paper as the "psycholotic" method. The combination of therapy and LSD, or any other psychedelic, would later be popularized as psychedelic psychotherapy. Twenty-seven of thirty patients with presentations more consistent with classic depression or anxiety disorders subjectively reported benefit. The final judgment of improvement overall was made by the clinician treating the patient. This study lacked a control group and was unblinded. There are no details of any worsening or adverse effects from the remaining patients[8]. In a follow-up study in 1957, the same researchers reported 93 patients with "severe neuroses", which would include a broad range of psychiatric illness, treated with LSD and then followed up in 6 months. 43% of patients improved, again to subjective report, unblinded, and without control groups[10]. In Australia in 1964, a control group was added during the treatment of 100 patients with an average of 3.28 LSD assisted psychotherapy sessions. Of the 100 patients, 49 had "psychoneuroses", 27 had "personality disorder," 21 "sexual disorder," and 3 "residual schizophrenia." "Positive outcomes" were seen in 47 of 100. The rate of success appeared to be higher in those patients who had a shorter duration of presenting illness. Approximately 75% of patients improved that had 0-2 years of diagnosed illness. In those with more than 21 years of illness, only 37% improved. Improvement was judged subjectively by the clinicians. No statistical results were published in this study[11].

By the 1960's LSD had become intertwined in the counterculture revolution in America and had become classified as a "psychedelic". Humphrey Osmond, an English psychiatrist, combined the words psyche (mind, soul, spirit) and delos (clear, manifest) in a letter to author Aldous Huxley. Aldous Huxley wrote a book detailing his experience with mescaline, *The Doors of Perception, 1954*. Aldous Huxley later took LSD and referred to his experience as "the direct total awareness from the inside"[12]. A perception of LSD had made its way into the cultural forefront and recreational use was encouraged by proponents of the counterculture movement by such notable figures as Timothy Leary. Due to such countercultural popularity, there was considerable difficulty in blinding patients to a powerful psychotropic substance especially with the cultural and social perceptions of the effects of the drug. Any prior perception of any drug may infringe on an individual's experience prior to ingestion.

In the 1960's and early 1970's, in Baltimore, Maryland a large range of studies were performed on the utility of psychedelics, at Spring Grove State Hospital and the Maryland Psychiatric Research Center. A total of 243 patients with non-psychotic psychiatric disorders, such as anxiety, depression, personality disorders, and alcohol addiction were studied[13]. LSD in this setting was administered in doses of 200-300mcg. This was sometimes combined with 200-400mg of mescaline. Emotional support was given in the form of a male or female sitter, but no formal structured psychotherapy or psychoanalysis was provided. Follow up was at 1 day, then at 1, 4, 8, and 12 weeks, and then at 6 months. Patients were given a retrospective

questionnaire that was completed by 93 patients in the sample. Results showed 83% reported "lasting benefit" which correlated with "a greater awareness of ultimate reality". The improvement rate was 76% at 1-3 months, 85% 3-6 months and remained at 85% at 6 months. Clinicians rated patients retrospectively with scores ranging from "worse, none, some, substantial, and marked". Per clinician ratings on all 243 patients, 81.1% improved to some degree. Only 2.1% were deemed to be "worse"[13].

In 1968, a study compared patients with schizophrenia and healthy controls who were randomly administered LSD. Based on a questionnaire, patients with schizophrenia who received LSD had worsening of symptoms. The same questionnaire was used for healthy controls who received LSD and they reported: "feelings of unreality", "loss of control", "changes in the meanings of experiences", and "suspiciousness" which more closely resembled paranoid schizophrenics. They also noted significant visual hallucinations during their LSD experience but with schizophrenics auditory hallucinations predominated[15]. In another notable study, LSD was given to 58 alcoholics on an inpatient unit in Ontario, Canada. This group was compared to 35 alcoholics in group psychotherapy and 45 alcoholics receiving "standard care". The standard care group was taken from patients of psychiatrists not connected to the study. Chi-square analysis reported significant differences in the rates of abstinence from alcohol in those given LSD compared to the group psychotherapy and standard of care cohorts. The methods of analysis and the p values were not stated in the study and the controls were not matched. Several other studies, primarily in Canada demonstrated some efficacy in the treatment of alcoholism, but with similar study design limitations[13].

Treatment of alcoholism with LSD in the late 1960's followed a more systematic approach insofar as study designs and quality are concerned. This is likely attributable to alcohol use disorder being easier to quantify and relies less on subjective criteria, than non-psychotic psychiatric disorders. Most initial studies were uncontrolled in the early 1960's. Out of those reporting "much improved" symptoms were 30 out of 41 alcoholics and 39 patients with other diagnoses who were given 400-1500mcg of LSD[16]. This study was similar to the earlier LSD studies with respect to no control group, no blinding, and subjective assessments. In 1969, at a Veterans Administration Hospital in California, 72 male inpatients with a diagnosis of alcoholism were randomized to LSD or placebo. The novel concept for placebo is significant in this study. The patients were randomized to receive either 600mcg of LSD or 60mg of dextroamphetamine. No psychotherapy was included, but the environment did allow for calm music and low lighting. A research assistant was provided as needed for reassurance. Baseline and follow up measurements were taken of drinking habits. A scale for drinking and the social consequences of drinking habits were recorded with a scale that was designed and validated for the trial. Data was collected prior to study and at 2, 6, and 12 months post-treatment by a blinded researcher to avoid bias. This researcher was independent of the initial study. Of 72 patients, 20 dropped out and an additional 27 patients dropped out by 6 months. Questionnaire scores were analyzed using Analysis of Variants (ANOVA), which showed that the LSD group was significantly improved compared to the dextroamphetamine group ($F = 8.5$, $p < .01$). This difference failed to be significant at the 6 months follow up. At the 12 months follow up, 17 patients were in the LSD group and 12 remained in the

placebo group and analysis was not considered relevant[17]. A meta-analysis of several studies, including the two mentioned above, demonstrated that LSD treatment was associated with sustained abstinence at 1-3 months (OR =2.07, 95% CI, 1.26-3.42; p = .004). At six months, there was found to be no statistical significance (OR, 1.42, 95% CI, 0.65-3.10, p =.38)[18].

Studies published before 1970, as discussed above, had several limitations. Treatment groups suffered from inadequate and inconsistent definitions, treatments were inconsistently defined, control groups were absent, non-blind studies were common, non-validated outcome measures were frequently used, adverse outcomes were poorly reported, and there was an overall lack of statistical analysis and statistical calculations of power[13]. Once LSD was defined as a schedule I compound, the amount of research declined substantially. The resurgence of research into LSD, and psychedelics, in general, has steadily garnered increased interest over the past 25 years.

LSD ASSISSTED PSYCHOTHERAPY

In 1959, two researchers compiled a framework of guidelines specific to LSD psychotherapy[19]. There has been no other attempt in the current literature to systematize LSD psychotherapy for the western world. Switzerland approved the use of LSD assisted psychotherapy in terminal cancer patients in 1973 with significant early work performed by Stanislav Grof, a Czech Psychiatrist. Swiss research into psychedelic assisted psychotherapy lasted from 1988-1993. In 1995, a follow-up study was conducted on 171 patients, of which 135 responded to the questionnaire, who had been administered either 3,4-Methylenedioxymethamphetamine (MDMA) or LSD in combination with therapy. The patients were selected from a group of three therapists who had held group therapy sessions. Elements of psychedelic therapy, as developed by Leuner, a German researcher, were used[13]. Recommendations for psychedelic therapy were to utilize low to medium dosage and incorporate a group setting in combination with continuous verbal therapy. This was then integrated with therapy as designed by Grof, on terminal cancer patients in 1973, which consisted of a high dose of LSD, with the use of music and silence. Depending on the therapist dosages ranged from 125mcg-400mcg. The duration of therapy lasted from 1 session to 3-9 years of treatment. Patients took part in an average of 70.3 non-LSD sessions and LSD sessions varied from 1-16. The questionnaire asked for a retrospective assessment of the patient's condition pre and post therapy. Patients listed reasons for interest in psychedelic assisted therapy and 57% reported self-exploration as the main reason. The most common diagnoses were personality disorder (38%), adjustment disorder (25.6%), and affective disorders (24.8%). Questionnaires demonstrated 64.5% had an "emotionally important" experience. Quality of life was rated as improved in 84.3% of patients. Better self-acceptance was reported in 81.1%. Only 2.5% reported decreased self-acceptance. Nicotine was used less frequently by 3.3% of patients, cannabis by 7.4%, alcohol by 19.8%. The results were limited based on design and retrospective reports but were consistent with the results of studies performed from 1988-1993. Similar studies with limited statistical significance have been done in the United States[20].

Blewett and Chwelos compiled guidelines for psychotherapy that remain similar to current modes of therapy, such as CBT, but with instructions specific to LSD guided therapy and detailed explanations for the clinician and the patient. In their paper, published in 1959, they discuss the

importance of set and setting in the administration of LSD and other psychedelics. With the initiation of therapy, they provide guidelines on the approach the patient must have:

"The patient must realize that his present methods of behaving are inadequate and unsatisfying to him personally."

"He must develop sufficiently strong motivation to carry him through the difficult and painful process of coming to understand and accept himself."

"On the basis of this self-understanding, he must learn how to alter his behavior to satisfy the new pattern of motivation which has developed out of self-understanding."

The nature of the experience is then described in detail. It is suggested that the role of the therapist is to act as a guide and they may consider taking a smaller dose of LSD, concurrently with the patient to foster a sense of "emotional sensitivity". The following description was taken from firsthand accounts of patients that had been studied and asked to describe their LSD experience and is paraphrased as follows:

1. The feeling of being at one with the universe
2. Experience of being able to see oneself objectively or that one has two identities
3. Change in the usual concept of self with a concomitant change in their perceived body
4. Change in the perception of space and time
5. Enhancement in the sensory fields
6. Changes in thinking and understanding so the subject feels he develops a profound understanding in the field of philosophy or religion or in a tendency to think analogically.
7. A wider range of emotions with rapid fluctuation
8. Increased sensitivity to the feelings of others
9. Psychotic changes: Illusions, delusions, hallucinations, influence, persecution, perceptual distortion, and severe anxiety

A few paragraphs outline the preparation of the patient prior to psychedelic administration. Preparation for the session includes writing an autobiography to gain a personal perspective prior to taking LSD. Individual versus group methods were left to the discretion of the provider but group sessions appear to have had more disadvantages and may have been "difficult and unnecessary", compared to individual 1:1 experiences. Group therapy may lead to a misinterpretation of feelings and should be cautioned against. Once the patient has completed these preparatory requirements only then should they be allowed to progress to the psychedelic experience. It is recommended that LSD be introduced gradually, at an initial dose of 100-200mcg or 300-600mcg but it is suggested to introduce at lower doses (100mcg). No specific regimen has been developed to determine the number of LSD sessions or the minimum pre and post treatment encounters necessary to lead to the most efficacious therapy outcomes. The recommendation is to use doses larger than 300mcg (up to 1000-1500mcg) in those with prior experience with LSD psychotherapy. The paper then outlines the stages of the experience numbered I-VIII and details each stage the patient may experience and provides insight into the role of the therapist in each stage. These descriptions are beyond the scope of this paper. Also provided is a summary of the problems in the assessment of improvement in patients undergoing LSD therapy due to the variability in symptoms and of the psychometric tools used to

measure change. The authors suggest a catalog of alterations in specific areas of behavior for the patient (on and off the drug), where the researcher should be concerned with physiologic changes or variance from previously administered objective test scores. A questionnaire could be administered at different times when using different doses to record and track responses. It is also suggested that patients would consider their emotional state during and after a session. Toward the end of the paper, the authors report "it is unfortunate that much of the present research aimed at quantification of the LSD induced change is dealing with extraneous or unimportant variables and is therefore largely irrelevant to any assessment of the therapeutic effect of the drug"[19].

NEUROSCIENCE

An objective assessment of the direct comparison of standard treatment (CBT, DBT, trauma-focused therapy, etc.) to LSD psychotherapy has not been performed. The question remains as to is the drug and therapy at all effective, less effective, or more effective than standard of care. The standard of care would also vary depending on the mental illness one would be attempting to treat. There is limited evidence to suggest that the novel state that psychedelics create is beneficial and most evidence is hampered by subjective rating systems and poor study designs. Certain theories of mind have been proposed that suggest the potential of these substances to induce neuroplasticity which may have additional applications for LSD assisted psychotherapy. The entropic brain hypothesis is one such theory. Entropy itself is defined as the dimensionless quality used for measuring uncertainty about the state of a system. It may imply disorder, as with "high entropy"[21]. It may be argued with the entropic brain hypothesis that entropy is suppressed in normal waking consciousness and that consciousness itself is a viewpoint of restraint. This is similar to Aldous Huxley's description of the "mind at large", where he viewed consciousness as controlled by a valve and that we only experience a portion of the larger mind[22]. These "larger mind" states may be primary states of consciousness. Entry into primary states (high entropy states) depend on a collapse of organized activity within the default mode network (DMN) and decoupling between the DMN and the medial temporal lobes (MTL). Normal functioning of the brain has low entropy of the DMN and significant coupling between the DMN and MTL[21]. A study performed with psilocybin and brain imaging was performed in 2014 with the aim to suggest a new theory of consciousness that would incorporate neurobiology, physics, and psychoanalysis. The entropic brain hypothesis proposes that the quality of any conscious state depends on the system's entropy measured by the parameters of brain function. System entropy is an idea used in physics and chemistry. Currently, system entropy of the brain has been emerging as a topic of interest in neuroscience. This idea is combined with the psychoanalytic theory of the mind in respect to consciousness and unconsciousness and the idea of the ego, superego, and id. In this study[21], the focus was on the ego. Brain entropy, theory of consciousness, and ego were related via the potential for new insights through the use of psychedelics. The effects of psychedelic substances on the brain are shown to induce high levels of entropy into the system. Psilocybin in this study was used, but the authors generalized the idea to extend to other typical psychedelics, such as LSD, by using psilocybin as the "classic psychedelic". The authors propose that the default mode network, resting state functional connectivity, and spontaneous, synchronous oscillatory activity in the

posterior cingulate cortex (specifically the alpha range of 8-13hz frequency band) are what they consider the "neural correlates of ego integrity". Ego integrity in the study is defined as the normal functioning of the brain system at a low entropy state in these specific areas that cultivates the formulation of the ego (or waking consciousness in an ideal healthy "normal" subject). To perform this grand feat, the researchers focused on the system level mechanics of the psychedelic states as an example of the primary states of consciousness (high entropy) that may also be observed in REM sleep and early psychosis. FMRI studies utilizing arterial spin techniques that measure changes in the cerebral blood flow of the brain were performed before and after intravenous (IV) administration of psilocybin or placebo. Psilocybin has a rapid onset when given IV, producing effects within seconds. Infusions occurred over 1 minute, starting at minute 6of an 18-minute resting-state scan. Decreased cerebral blood flow was noted in key regions of the default mode network. These findings were replicated using Blood oxygen level dependent (BOLD)signal MRI scans with the same infusion times in healthy volunteers. The BOLD signals were consistent with cerebral blood flow decreases found in the DMN. In addition, they were able to perform resting-state fMRI, which is a technique used to map the brain and evaluate reaction regionally when an explicit task is not being performed which is used to reveal the connectivity of brain structures that may not be apparent using other fMRI techniques. Connections between the medial prefrontal cortex, right front middle gyrus, and bilateral hippocampus all showed a decrease in connectivity as compared to baseline samples when psilocybin was used. This suggests an increase in the entropy of these systems thought to modulate a large portion of the average experience of consciousness[21].

The DMN regions, in general, receive more cerebral blood flow and have higher metabolic rates than other regions of the brain. In the posterior cingulate cortex, rates of metabolism are approximately 20% higher than the rest of the brain. DMN regions are a highly interconnected region of the brain and in some studies referenced by Carhart Harris, it may be considered to have the highest level of functional hierarchy and serves as the "orchestrator or conductor" of global brain function[23]. However, its' functionality is removed from sensory processing, which suggests that this portion of the brain may have more to do with awareness concerning theory-of-mind, self-reflection, mental time travel or other "metacognitive" processes. It is still poorly understood as to why this region of the brain consumes the most energy[21].

The medial temporal lobe circuits, which include the hippocampus, show decreased coupling between the MTL and the DMN under the influence of psychedelics, while BOLD signals after psilocybin administration increased almost exclusively in the hippocampus. Additional studies reviewed by Carhart Harris demonstrated similar findings in LSD, REM sleep, and early psychosis. These findings are suggestive that coupling between the MTL and the cortical DMN is important to "normal" functioning and becomes desynchronous and disorganized in the setting of psychedelic use, which leads to high fluctuations in cerebral blood flow in the hippocampus[21].

BOLD activity in the DMN has been shown to be related to alpha oscillations in the brain. This is the dominant finding on EEG in the frequency of 8 to 13 Hz that can be found in a normal awake state, relaxed with the eyes closed. Pyramidal neurons are known to express numerous 5-

HT2A receptors, which are known to intrinsically fire at an alpha frequency. 5-HT2A receptors are an important target of psychedelics and were found to have decreased in "alpha power" on fMRI after psilocybin administration, which positively correlated with "ego-disintegration" as measured by a 23-point subjective rating scale post-administration. Despite all the findings that the DMN increased in entropy and cerebral blood flow decreased or varied significantly; during the use of psilocybin the DMN still maintains the most blood flow, as compared to anywhere else in the brain. This is suggestive of the conductor role, or the "seat of the ego" that the DMN plays in the brain[21].

LSD PHARMACOLOGY

LSD is considered a semisynthetic substance, derived from naturally occurring lysergic acid from the parasitic rye fungus *Claviceps purpurea*. There has been no recorded evidence of physical damage from LSD, but several older studies demonstrated psychiatric complications in "normal patients", as was previously mentioned, but especially in patients with psychotic disorder. The molecule is an indole with a tetracyclic ring with carbons 5 and 8 being asymmetric, which means there are d- and l- isomers. Interestingly, only the d-isomer has psychoactive properties. LSD is water soluble and stabilized in solution. A dose of 75mcg-150mcg is known to alter consciousness significantly. The experience is characterized by euphoria, elevated sense of connectivity, enhanced self-reflection, hallucinations, synesthesia, illusions, change in time perception, mood swings, changes in body image, changes in ego function. Dysphoria and psychosis have been reported. The psychological effects may last from 6-10 hours and the duration of the experience is dose dependent. The minimal recognizable dose is 25mcg in humans. Traumatic "bad trip" experience may have long lasting effects such as mood swings and flashbacks, or what is commonly known as hallucinogen persisting perception disorder. Some studies show learning processes to be unaffected by 75-100mcg. Other studies have demonstrated decreased attention and concentration tasks on 100mcg with impaired recognition and recall. Autonomic effects may occur in humans, such as mydriasis, diaphoresis, tachycardia, tachypnea, hypertonia, hyperglycemia, lower blood pressure, increase in body temperature, salivation, nausea, emesis, flushing of the face. Tolerance develops after a few days of "moderate doses" (5-100mcg) with an average of 2-3 days. After tolerance is established, it typically takes 4 days to resolve allowing for the full effects to manifest again[24].

The LD_{50} is an assessment of safety used to determine the lethal dose (LD) required to kill 50% of the test population, usually calculated by weight. The LD_{50} of LSD is variable between species. Rabbits are the most sensitive with an LD_{50} of 0.3mg/kg IV. Rats have an LD_{50} of 16.5mg/kg IV, mice have an LD_{50} of 46-60mg/kg IV. For humans, there has been no documented death attributable to LSD overdose. There have been eight individuals who accidentally consumed a dose of LSD intranasally and had plasma levels of 1000-7000mcg per 100mL. These patients suffered from comatose states, hyperthermia, vomiting, gastric bleeding, and respiratory problems, but all survived without any known long-term complications. LSD showed some teratogenic effects in mice, rats, and hamsters in incredibly high doses of 500mcg/kg and the most susceptible period in mice was in the first seven days of pregnancy. No carcinogenic potential for LSD has been found[24].

LSD is distributed in the body across all organs and tissues, but no definitive levels have been estimated per organ system in humans. LSD may act on the excretion of inorganic phosphate and may facilitate the binding of phosphate. LSD does not affect biologic amine excretion. In humans, LSD has a slight decrease in creatinine clearance, but no change in calcium clearance or serum calcium levels. No changes found for serum creatinine, plasma urea, or plasma sodium, chloride, cholesterol, total lipids, or osmolality. LSD administered before or 1 hour after sleep onset increased total REM sleep and demonstrated a prolongation of REM periods and shorter intervals between periods. Theta activity is increased. Prolactin levels are lowered in male rats following LSD administration, no findings have been done in humans. When LSD is ingested with a large meal, plasma levels may be decreased. The pH of the stomach and duodenum will influence the absorption of LSD. No effect on liver function has been found. LSD may exaggerate the reflex response in deep tendon reflexes. LSD may be detected via high-performance thin-layer chromatography and mass spectrometry. It may be detectable in the plasma within 6-12 hours and 2-4 days in the urine. LSD detection in hair specimens is available but cannot detect metabolites[24].

LSD acts on serotonin receptors that are currently thought to be predominantly 5-HT1A and 5-HT2A, the 5HT2A receptor is attributed to the hallucinogenic effect. LSD is thought to have the potential for antidepressant-like effects due to its modulation on the serotonergic system. 5-10mcg were injected IV into rats and showed 5-HT spontaneous firing activities that were prevented by administration of a 5HT-1A antagonist post dosage. In vitro studies show that LSD binds cloned human 5HT1A and selective 5-HT2A receptors, this affinity for 5-HT2A has been demonstrated in male rats consistent with the action of a partial agonist. Postsynaptic 5HT2A receptors in layer V of the medial prefrontal cortex are thought to be responsible for the hallucinatory aspects. The 5HT2a modulation of LSD may influence downstream expression and modulation of genes. This effect on gene expression has the potential to induce neuroplasticity and long-term neurochemical changes[25]. LSD has also been found to act on 5-HT1A, 5-HT1B, 5-HT2C, 5-HT-1D, 5-HT1E, 5-HT6, 5-HT7[24].

Animal studies have demonstrated glutamate plays a role in several downstream effects of LSD. Some effects on the D4 receptor have been found, but the studies are small and limited. Postsynaptic cortical 5-HT2A receptor agonism increases cellular glutamate release in the synaptic clefts as well as a time dependent increase in glutamate in the prefrontal cortex. Slice preparations of rat pyramidal neurons, high in serotonin receptor, demonstrate that low concentrations of serotonin modulate NMDA receptor activity. This is similar to ketamine, a dissociative anesthetic, that modulates NMDA activity. Dopamine is thought to be at least partially responsible for the psychosis mimicking state of all classical psychedelics. At higher doses, 60-120mcg caused a dose dependent decrease in dopamine in the ventral tegmental area. Administration of Haldol, a dopamine antagonist prevents the inhibition by LSD of the Ventral tegmental area. In vivo, LSD was found to lower prolactin, suggesting but not confirming, a role in the modulation of the dopaminergic system. TAAR1 receptor is an important modulator of both dopamine and serotonin and abnormal levels have been implicated in schizophrenia. LSD has a high affinity for the TAAR1 receptor in rats. No known effect was seen with humans. Future research could

determine if there is an effect that is modulated directly or downstream by LSD on the TAAR1 receptor[25].

DISCUSSION

Medical applications of a psychedelic substance, at first glance, seem to be wrapped in its own form of mysticism, with an idea similar to the writings of William Blake, "If the doors of perception were cleansed everything would appear to man as it is, infinite. For man has closed himself up, till he sees all things thro' narrow chinks of his cavern[26]." LSD is a powerful psychotropic substance and humans have been using psychotropic substances culturally, spiritually, and recreationally since their discovery. The potential for psychotropics has gained interest with the advent of the use of ketamine for treatment-resistant depression. Psychiatry has reached a pharmaceutical plateau in terms of powerful antidepressants. Should LSD prove useful and gain approval for more study, it would be impossible to administer the drug in a clinical setting without at minimum, supportive therapy. This supportive therapy alone would be confounding, as there would be little in the way of standardizing a definition of supportive therapy that would not interfere with the patient's perception of the experience. Depression is a state of rigid and inflexible thinking in which the patient's thought processes are almost entirely inwardly self-critical. People suffering from depression may be unable to remove themselves from this fixed state, making depression incredibly difficult to treat. This same statement may be applied to PTSD, addiction, personality disorders, or anxiety. The DMN is strongly implicated in the process, with its proposed link to self-introspection. Primary states of consciousness may be more amenable to disrupt stereotyped and fixed patterns by physically disrupting critical brain connectivity and their patterns of activity. Psychedelics may be therapeutic in their ability to return the brain to more primary or entropic states. It may also lower repression and increase access to the "psychoanalytic unconscious" by breaking down the brain's normal hierarchy of connectivity structures[21]. Modalities such as transcranial magnetic stimulation (TMS) or ketamine are newer treatments for resistant depression, but with only recent and limited evidence to support their use. Antidepressant research with psychedelics has been mainly done in recent years with psilocybin and demonstrates promising results. In 2014, a double-blind, placebo-controlled study was performed with LSD assisted psychotherapy for the treatment of anxiety and depression in patients with life-threatening disease[25]. Patients were given 200mcg LSD or low dose LSD 20mcg for placebo in two sessions 4-6 weeks apart. The LSD (200mcg) group demonstrated reduced depressive symptoms two months after the second administration of LSD. This improvement lasted up to 12 months post dose[27].

In conclusion, it remains unclear whether LSD has a medical utility to treating mental illness at this time. More high-quality research is needed to determine the utility of the potential demonstrated in these early studies. The future of LSD may not return the promise of this early and limited evidence, but the idea of a compound that can disrupt critical brain neuroconnectivity with no known adverse long-term effects and relatively safe profile deserves more attention.

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Case Report

Introspective Acceptance of Gender Identity: Case Report Detailing Resolution of Gender Dysphoria After Use of LSD

Joseph Pullara, M.D.

Gender dysphoria is a rare psychiatric disorder that has traditionally been managed and treated using hormone replacement and intensive plastic surgery. Most psychiatric medications and therapies offer little benefit in regards to the symptoms of gender dysphoria and instead are initiated to treat associated conditions such as anxiety or depressive disorders. This report describes the case of a 32-year-old male patient with a long-standing history of Gender Dysphoria (GD) who had symptoms almost completely resolve after orally ingesting 300 micrograms of Lysergic Acid Diethylamide (LSD). This case serves to provide evidence in support of LSD as an effective psychotherapeutic treatment modality.

CASE REPORT:

Jordyn was a 32-year-old male patient with a history of Gender Dysphoria (GD), borderline personality disorder (BPD), post-traumatic stress disorder (PTSD), generalized anxiety disorder, and persistent depressive disorder who began following with outpatient psychiatry services after an inpatient psychiatric admission for suicidal ideations. At the time of his inpatient admission, he had developed an elaborate plan to shoot himself in the head with a handgun. He had a history of multiple admissions for similar reasons and had failed numerous psychotropic agents from various pharmacologic classes.

He agreed to a trial of psychotherapy with this author shortly after discharge from the inpatient psychiatric unit. Over the course of a year, a therapeutic relationship was established through several psychotherapeutic sessions that focused on cognitive-behavioral interventions for his symptoms of anxiety and depression. His chief complaints typically were about his gender dysphoria and overwhelming anxiety. He described deep feelings of neurotic distress centered around being "outed." He initially dressed in a very feminine manner and spoke in a purposefully feminine tone of voice. He preferred the pronouns "she, her and hers." To his friends and co-workers, he was looked upon as a female. He considered himself to be transgendered but held strong disdain for other transgender individuals. He constantly worried that co-workers or strangers in public would recognize him as male.

His struggles with gender dysphoria dated back to age 5 when he first recalled not feeling "normal." As a child, he often wanted to join in activities with his twin sister: wearing dresses, playing on the softball team (instead of a baseball team), and having sleepovers with other girls. His father was a Navy veteran who served in Vietnam and did not approve of these behaviors. His mother noticed that Jordyn struggled with his gender identity and was more supportive, which drew a divide in their household. One summer, his father enrolled him in a local "gay conversion camp" in an effort to "teach [him] how to be a man." This caused him to question his gender identity throughout childhood and into his teenage years. In high school, he went through a phase where he tried to prove his masculinity to all of the other high school boys and became heavily

invested in stereotypical male topics: cars, sports, women. This eventually culminated in him having sex with a woman he was friends with, in an effort to "prove" to his peers that he was a man. This encounter resulted in the woman getting pregnant with his only daughter, and their families pressuring them into getting married.

Though their marriage was unconventional, he had been very honest with her about his attraction to other men, and his thoughts about his gender identity. They mutually came to an agreement in which Jordyn could engage in relationships with other men, but should he begin to transition the marriage would have to end immediately. This agreement lasted for a few years, but eventually, Jordyn's distress about his gender identity became too much and he made the decision to begin the process of transitioning thus ending his marriage. He began to socially transition first by wearing traditional female attire and using make-up to appear more feminine. After this period, he sought evaluation and elected to begin medically transitioning and was started on hormone replacement therapy with estradiol, finasteride, and spironolactone. Prior to our therapeutic relationship, he had been seen by two licensed psychologists as part of the evaluation process for a future gender reassignment surgery. Since he was a child, he strongly disliked his penis and had frequent intrusive thoughts of harming his penis or removing it. He had gone so far as to remove mirrors in his house so that he would not have to accidentally look at it. Gender reassignment surgery was something he had sought for as long as he had known it was a potential treatment option.

His thoughts on what would happen after the surgery were intricately detailed but cognitively complex. He stated that he knew he would never be biologically female. He understood that he would never lactate or bear children. He believed he would always consider himself a transwoman, and never planned to consider himself female. He did not worry that he would not like the aesthetic outcome of the surgery due to both the level of repulsion he maintained for the appearance of his current genitalia and because he had looked through hundreds of post-operative photos online. He frequented online forums to read other individual's reports of detransitioning and adverse emotional outcomes from the surgery and was sure that he would not experience these same issues because of his beliefs and understanding that he would never be a biological female. After taking all of these factors into consideration and receiving the approval of all medical specialties involved in the gender transition process he elected to schedule a date for gender reassignment surgery and started making the necessary preparations to schedule time off from his work for the procedure and post-operative recovery.

Interestingly, one afternoon he presented to the psychiatry clinic in unrecognizable attire. He had cut his hair short, started growing facial hair, and was dressed in traditionally male attire. He asked to be referred to by male pronouns and had been conducting his life as a male. When asked what had changed from his previous psychotherapy session just two weeks prior, he described a very influential psychedelic experience that occurred under the influence of Lysergic Acid Diethylamide (LSD).

Though he had experimented with LSD a few times previously, this experience was substantially different. Earlier in the morning, he had orally ingested 300 micrograms of LSD with the intention of going to a music festival with friends. He started to feel the peak effects of LSD around the time he arrived at the music festival. He vividly recalled standing in line at the festival, watching people walk past him. Previously, this was a large source of

anxiety for him because he constantly worried that people would notice he was a transgender individual. This would lead his mind to race with thoughts and fears that people would discover his "secret identity," and therefore try to harm him. While under the influence of LSD, these neuroses were significantly diminished. He reported seeing himself from a third-person perspective, merely existing in the world. He realized that people were not looking at him, nor did they recognize his presence around them. This reduction in egocentric thinking due to the realization that he was unimportant to these individuals was incredibly freeing for him.

After the effects had worn off, he spent time reflecting on the experience. He came to discover inner peace within himself as he felt that he had seen his true self for the first time. He began to question himself: "How can I expect the world to accept me when we I cannot even accept myself for who I am?" He did not remember where he had heard that phrase, but it greatly impacted him. He decided that he no longer wished to pursue hormone replacement therapy or gender reassignment surgery and desisted in his transition.

DISCUSSION:

To this author's knowledge, there are no other case reports of LSD being used as a psychotherapeutic modality to treat gender dysphoria. A significant amount of research has been done on LSD's effect on depression, PTSD and alcohol use disorder which have shown promising results[1]. This case report serves to add to the literature and suggests possible efficacy in treating this complex disorder. In this case, LSD provided the patient with novel insight into his dysphoria that he had not previously been able to achieve with traditional psychotropic medication or psychotherapy. He was able to find the root cause of his gender dysphoria through self-reflective introspection from a third-person perspective. In the months after this LSD experience, he has remained firm in his intentions to desist and has lived his life in a traditional male role.

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Psychedelic Assisted Psychotherapy for the Treatment of Gender Dysphoria

Tyler R. Kjorvestad, M.D.

In this issue, Pullara [1] describes the case of a young adult male patient who was diagnosed with Gender Dysphoria (GD) and who had begun the process of both socially and medically transitioning. This transition period was marked by intense feelings of emotional distress, anxiety, depression, and suicidal thought processes, which are all too common among individuals diagnosed with GD [2]. The patient acting on his own and without proper medical supervision, which this journal does not endorse, took $300\mu g$ of LSD and had a meaningful psychedelic experience, which caused the temporary resolution of his suicidal thoughts and led to the decision to completely desist in the transition process. To our knowledge, this is the first-ever reported case in which symptoms of GD have been improved or resolved after the use of a psychedelic substance.

Despite an estimated prevalence of 390 cases per 100,000 adults in the US [3], GD remains both a highly contentious and disproportionately discussed subject not only within the world of Psychiatry but in society at large. Relative to other psychiatric conditions, there exists only limited long term evidence for the current treatment regimens of hormone replacement therapy (HRT) and gender reassignment procedures (GRP). Further research will be needed and is currently on-going to determine whether the outcomes of these interventions have been successful. Successful studies will have to adequately control for confounding variables like the known comorbidities of GD which include: childhood maltreatment [4], substance use disorders [5,6], physical or emotional abuse [7], personality disorders [8,9], sexual assault or abuse [4,10], and other psychiatric conditions such as depression and anxiety[8,11,12]. Also, there has been a reported increase in GD among females diagnosed with Autism Spectrum Disorder (ASD) [13], which raises the concern for social contagion like effects among this vulnerable population. All of this information ultimately leads one to question whether one size fits all treatment regimen of HRT and GRP is appropriate for every individual diagnosed with GD or whether an alternative approach aimed at addressing those aforementioned issues would be more prudent.

Desistance rates, per the *Diagnostic and Statistical Manual of Mental Disorders* (DSM) *V*, for individuals diagnosed with GD in childhood or adolescence, is at least 70% and reportedly as high as 98% in natal males and at least 50% and as high as 88% in natal females [14] by age 18 when this cohort is not started on HRT. Couple this with additional studies that show desistance rates of 73-98% [15,16,17], and it is clear that a majority of children and adolescents diagnosed with GD will remit by adulthood provided that no significant interventions are undertaken. However, this means that a not insignificant percentage of individuals will continue to suffer from the symptoms of GD and will require further treatment and management. Both HRT and GRP have shown mild to moderate improvements in certain symptoms of GD, specifically self-reported feelings of gender dysphoria, quality of life metrics, and psychosocial function [18]. Unfortunately, other large-scale, long-term studies looking at the objective measures of psychiatric morbidity, suicidal

behaviors, and mortality have shown that individuals who underwent HRT and GRP were still at a substantial risk.

One study showed that post-transition patients were at an almost three times higher risk of all-cause mortality, an approximately four times higher risk of psychiatric admission, and 19 times higher risk of attempting suicide [19]. Additionally, HRT has several risks associated with its use, including an increased risk of myocardial infarctions in female to male GD patients [20] and an increased risk of cerebrovascular accidents and venous thromboembolism in male to female GD patients [20,21]. Long term data on the effects of HRT is also lacking because most studies only obtain data and results from a 6-12-month period with only a few studies reporting data from patients who have been on HRT for greater than five years [22]. These studies, like most studies on GD patients, suffer from several methodological flaws stemming from small population sizes that result in underpowered studies, response bias due to the utilization of self-reported surveys, and moderate to large attrition biases. GRPs are also associated with several significant post-operative conditions such as normal general surgical risks of infection, bleeding, and adverse reaction to anesthesia. Additionally, GRP can also result in genitourinary and sexual dysfunction, wound healing disorders, gastrointestinal injuries to the rectum or colon, nerve injuries, disappointment in cosmetic appearance, and possibly minor or major regret [23,24]. Though with improved surgical techniques, the incidence of these complications is becoming less frequent.

While these results are far from conclusive, it does not mean that adequately screened and selected patients with GD would not benefit from HRT and GRP. The adverse effects of HRT and GRP do, however, raise the question of how to best manage the remaining patients with GD who, if started on HRT and GRP regimens, would be more likely to have adverse outcomes and less likely to benefit. It is in this patient population that psychedelics like Lysergic Acid Diethylamide (LSD) and Psilocybin might be able to offer an additional treatment option. Psychedelics have shown significant promise in the treatment of treatment-resistant depression [24,25,], PTSD [26], and suicidal ideation [27] and it is reasonable to hypothesize that if they were used therapeutically, in appropriately chosen patients suffering from GD that they may offer a benefit insofar as they could potentially lead to an improvement or resolution of the feelings of GD or, at the very least, mitigate symptoms of associated comorbid psychiatric conditions.

The prospective use of psychedelics for the treatment of GD is also in line with previous research investigating the potential use of psychedelics for the management of eating disorders like Anorexia or Bulimia Nervosa [28], Body Dysmorphic Disorder [29], or Obsessive-Compulsive Disorder (OCD) [30]. All of these conditions involve distressing feelings caused by either false beliefs about one's body image or an inability to quell obsessive thoughts, which are similar to some extent with the symptoms experienced by patients with GD.

Classic psychedelics, such as LSD, Psilocybin, Mescaline, and DMT, exert their neuropharmacological effects on the brain via binding to serotonin receptors, specifically $5HT_{2A}$, causing a neurochemical cascade [31,32] culminating in alterations to Resting State Networks (RSN). RSNs are "structured patterns of resting-state functional connectivity" regions of the brain that are highly active during perceptual or cognitive performance tasks [31,33]. The Default Mode Network (DMN) is one such RSN and is more active in the absence of goal-directed activities and "metacognitive" processes that are hypothesized to be

at least partially implicated in the formation of the "ego" [31,34,35]. The major neurochemical effects of the classic psychedelics appear to decrease or weaken activity in the DMN [31,36] and overall increase connections and activity between different RSNs [31,37] resulting in the prototypical subjective experiences of perceptual disturbances, increased emotional access, and ego dissolution. With ego dissolution being a significant predictor of positive experiences [31]. Ego dissolution and increased emotional access to feelings of forgiveness, trust, empathy, and acceptance are the two most promising factors with implications for the treatment of GD. For the subset of GD patients who, as previously mentioned, have co-morbid psychiatric conditions, suffer from substance use disorders, or experienced significant trauma or abuse the potential benefits from increased emotional processing and decreased ego interference due to the effects of a psychedelic substance could be sizeable, especially when used in association with psychotherapy, because of the high degree of emotional dysregulation and immature ego defense mechanisms that are commonly seen in these types of individuals.

Psychedelic use is contingent on the mindset of the patient, which is at least if not more important than the physical setting in which the experience takes place. The mindset is established in the weeks or months before the experience. This preparatory work gives time for the patient and the therapist to develop a therapeutic rapport, which is the most important aspect of psychotherapy, and without which an experience should not be attempted. During this preparatory phase, a patient's biological and psychosocial factors that could potentially result in a negative experience are noted. The patient is also encouraged to reflect on their life and, if feasible, write an autobiography. At the very least, a patient should develop a list of questions surrounding a particular problem for which they would like answers [38]. These activities prime the mind for the psychedelic experience, which reduces the likelihood of a negative experience.

The combination of psychotherapy in conjunction with Psychedelic substances often results in a rapid and deeply significant psychological experience that is associated with improvement or resolution of the prespecified intention of the session. The implications for use in GD patients are vast, but at a minimum, psychedelics could offer diagnostic clarity in patients with unclear GD diagnoses. For patients in whom the symptoms of GD seem to be inconsistent or questionable compared to the clinical picture or patients with significant co-morbid conditions such as ASD, OCD, PTSD, or personality disorders. Especially if there is a concern that these conditions are exacerbating GD symptoms, which decreases the likelihood that a patient would be able to complete the standard regimen of HRT and GRP. Additionally, psychedelics could help determine the primary driver of symptoms, if there is a concern that the GD is not the primary diagnosis but rather a manifestation of some underlying conditions such as the social contagion effect seen in ASD patients with Rapid Onset GD [4].

Psychedelics offer an alternative approach that could be used in GD patients to further assess their appropriateness for HRT and GRP in the one to two years before the initiation of this process. This would theoretically reduce the rates of regret post-transition that some patients with GD experience. Psychedelics are extremely safe, and when done in appropriate settings with adequate supervision, there is little risk of negative experiences or adverse events. However, some patients should not use Psychedelic substances, specifically

those with a psychotic illness such as Schizophrenia, Bipolar I Disorder, and similar psychotic illness. Beyond these exceptions, Psychedelics can be used in most patient populations with the caveat that thorough histories should be obtained with particular attention paid to screening for cardiovascular disease and family history of severe psychiatric illnesses. Medication reconciliations are imperative to reduce and avoid adverse drug events such as serotonin syndrome. Administration facilities should be equipped to handle common adverse events such as anxiety, nausea, or paranoia and develop contingency plans for severe reactions or behaviors [39]. Lastly, the potential of developing Hallucinogen Persisting Perception Disorder (HPPD) is relatively rare, with an estimated prevalence of around 4%. While it is theoretically possible to develop HPPD after any use of a hallucinogen or psychedelic, it is more common in frequent heavy users and relatively rare in clinical trial data where psychedelics are used at appropriate doses and intervals [40].

Psychedelics offer a potentially novel treatment modality for persons diagnosed with GD who, after appropriate psychiatric evaluation, are thought to incur far more risk than benefit in the current standard regimen of HRT and GRP. GD patients with co-morbid substance use disorders, a history of previous trauma or abuse, chronic suicidal thoughts, and or other psychiatric conditions, could likely benefit from Psychedelic associated Psychotherapy when it is utilized in an evidence-based manner with patients who are in the proper mindset and physical setting to best facilitate a positive and productive experience.

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Article

Psilocybin Use in the Future Psychiatric Practice: A Comprehensive Review

Anthony Ceman, M.D.

Objective: Psilocybin, the psychoactive compound found in "magic mushrooms," is currently a Schedule I substance; as such, the United States Federal Drug Administration consider it to have a high potential for abuse and no medical benefit. However, recent research using psilocybin for the treatment of psychiatric disorders has shown that in certain conditions, it may have superior efficacy with fewer adverse effects than current psychotherapeutic agents. A review of the literature was conducted to elucidate the benefits of psilocybin further and explore the possible implication of future clinical use.
Search Methods: Pubmed search terms: psilocybin and depression, anxiety, alcohol, alcohol cessation, and mechanism of action, which resulted in 187 articles with 22 being selected for review.
Results: Severe studies with smaller sample studies have shown positive results in the use of psilocybin in treatment-resistant depression, anxiety and depression associated with advanced-stage cancer, along with alcohol and tobacco use disorders. Limited, but positive data show possible treatment use in OCD and anxiety disorders.

INTRODUCTION

Psilocybin is a naturally occurring compound found in approximately 200 different species of mushrooms that naturally exist in North and South America, along with several areas in Europe, Africa, and Australia[1]. Psilocybin is considered a hallucinogenic agent and has been classified as a Schedule 1 substance by the United States Drug Enforcement Agency (DEA). A Schedule 1 substance is defined as a substance with high abuse potential, no currently accepted medical use, and has no documented and accepted safety data[2]. Given this, it is a felony to knowingly purchase, possess, distribute, or use any amount of psilocybin and is punishable by a fine of $5,000 and up to a year in prison on a federal level.

Psilocybin and other hallucinogens are substances that alter reality, perceptions, and visual, auditory, olfactory, and gustatory sensations. Despite the name, hallucinations typically do not occur, and therefore a more appropriate name is psychedelics from the Greek meaning 'mind-manifesting[3]. Biochemically psilocybin is a tryptamine alkaloid and is structurally similar to serotonin[4].

Once ingested via oral consumption, the compound psilocybin is quickly digested into psilocin, a compound that can cross the blood-brain barrier via the enzyme alkaline phosphatase and nonspecific esterases. Further metabolism occurs via monoamine oxidase and aldehyde dehydrogenase enzymes in the liver**.** Psilocin is structurally similar to serotonin and temporarily increases levels of serotonin in the brain[3]. Serotonin is widely implicated in numerous psychiatric conditions and agents that modulate serotonin improve the symptoms associated with these conditions. Therefore, because psychedelics, including psilocybin, alter serotonin pathways, it is reasonable to hypothesize that they could be utilized as a treatment modality. Emerging evidence supports this hypothesis with

psilocybin being used in the treatment of treatment-resistant depression, anxiety or depression associated with terminal illnesses, and tobacco and alcohol use disorders[5]. Psilocybin's psychedelic effects are thought to contribute to its efficacy by inducing personally meaningful and spiritually significant experiences that result in positive changes in cognitive processes and behaviors. These effects are not exclusive to individuals with psychiatric illness, as Griffins et al. noted in a 2006 study of 30 volunteer subjects who were administered psilocybin, achieved a psychedelic experience, and continued to report positive outcomes at the 2 months follow up[6]. These findings have significant implications for the future use of psychedelics as psychopharmacologic agents and as adjuvants to psychotherapy.

Figure 1:

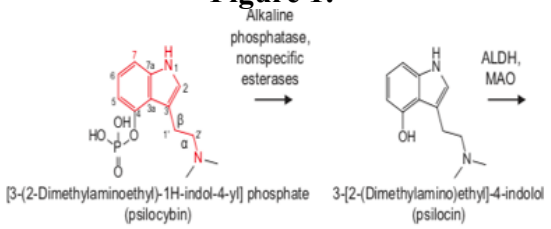
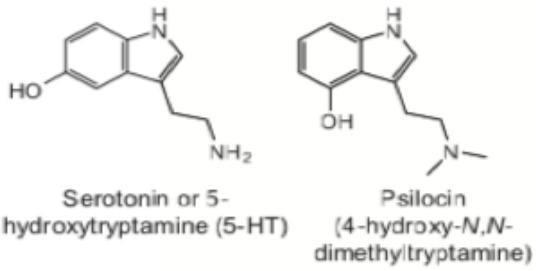


Figure 2:



SEARCH METHODOLOGY

This review included all studies published on the use of psilocybin for the treatment of psychiatric illness until September 1st, 2019. These studies included review articles and controlled trials. Search terms used included: psilocybin and depression, anxiety, alcohol, alcohol cessation, and mechanism of action. This query resulted in 187 articles with 22 being selected for the

MECHANISM OF ACTION AND SAFETY

Madsen et al. hypothesized that Psilocybin exerts its effects via Serotonin modulation by binding to the 5HT2A receptor. They also attempted to determine if there was a relationship between psilocybin ingestion and serotonin receptor occupancy. The study consisted of 8 participants that each had a baseline Positron Emission Tomography (PET) scan with a radio-labeled 5HT2A receptor ligand and then two subsequent PET scans following administration of psilocybin at doses ranging from 3-30mg. Following the administration of psilocybin, each participant underwent a follow-up PET scan (PET-1) 1 hour after consumption. Subjects 1-5 underwent a second follow-up PET scan (PET-2) later that same day. Table 1 indicates that increasing doses of psilocybin lead to higher receptor occupancy. This study showed that there was a significant increase at all doses of Psilocybin with a range in percent increase in serotonin occupancy from 42%-72%.

Table 1

Table 1. Descriptive data related to psilocybin interventions and corresponding 5-HT2AR occupancy estimates

ID	Dose (mg)	Weight-adjusted dose (mg/kg)	C_{max} (μg/L)	Mean psilocin PET 1 (μg/L)	Mean psilocin PET 2 (μg/L)	Occupancy PET 1 (%)	Occupancy PET 2 (%)
Subject 1	3	0.05	2.3	1.9	<LOQ*	42.9	1.8
Subject 2	6	0.07	4.4	3.5	0.7	56.2	26.7
Subject 3	12	0.14	16.7	12.6	3.4	66.4	42.9
Subject 4	15	0.2	11.7	10.5	2.3	63.2	30.9
Subject 5	18	0.2	11.8	10.6	2.6	72.4	47.0
Subject 6	24	0.27	12.0	9.0	NA	60	NA
Subject 7	24	0.3	18.9	11.5	NA	66	NA
Subject 8	30	0.3	19.3	15.6	NA	65.2	NA

*Below level of quantification

The safety profile for psychedelics, including psilocybin, is discussed in detail below. Common adverse effects include headaches, nausea, confusion, and hypertension all of which are generally self-limited to the psychedelic experience[7]. A study of 130,000 adults did not find an

association between lifetime use of any psychedelic substance and the chance of suicidal thoughts[8]. In regard to the unpredictable and erratic behavior that is occasionally portrayed in the media, Honyiglo et al. details in a 2019 case report the history of an 18-year-old who was intoxicated on psilocybin mushrooms and jumped out his second-story window to his death. He had no other psychoactive substances in his system, and his blood and urine were positive for psilocybin; thus, his death was attributed to his fall, and the fall was attributed to the use of psilocybin. This report demonstrates that although in a controlled environment, there is no evidence of addiction, tolerance, or withdrawal effects when used in an unsupervised setting psilocybin, can result in adverse outcomes, and it is therefore essential these medications only be used in appropriate clinical situations[9].

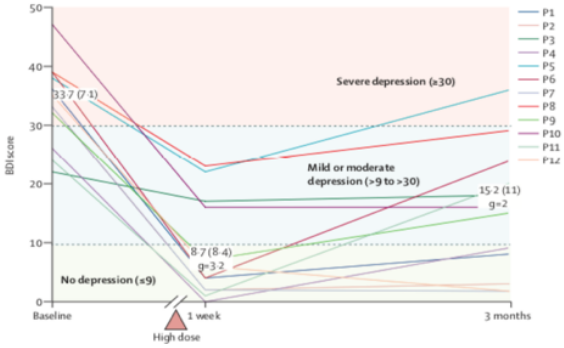
DEPRESSION

Major depression is defined as a constellation of symptoms consisting of depressed mood or anhedonia most days for at least 2 weeks, along with at least four contributing symptoms during this same time frame including weight changes, sleep changes, psychomotor agitation or retardation, changes in energy, feelings of worthlessness or guilt, concentration issues and recurrent thoughts of death[10]. In 2018 the Federal Drug Administration (FDA) examined the data associated with psilocybin therapy for treatment-resistant depression and allowed it to progress to phase II clinical trials[11].

Carhart-Harris et al., in 2016, details treatment-resistant depression and the response to psilocybin therapy; in this study, 12 patients were recruited who were screened with a Hamilton Depression Rating Scale (HAM-D) and scored in the moderate to severe range or above 17 on the scale. Once enrolled in the study baseline, Beck Depression Inventory (BDI) and Quick Inventory of Depressive Symptoms (QIDS) were obtained. The participants were required to have failed at least a 6-week trial of two separate antidepressants during the current depressive episode. Exclusion criteria in the study were current or previous psychotic disorder, family history of psychotic disorder, a medical condition that is not suitable for study, serious suicide attempt that required hospitalization, history of mania, needle phobia, positive pregnancy test or current alcohol or drug dependence. The Psilocybin was obtained from THC-Pharm in Germany and formulated into capsules. Each participant underwent a 4-hour preparatory session to try to identify the cause of their depression and discuss the effects of psilocybin during the dosing session. The administration protocol consisted of a low dose, 10mg, and was followed by a higher dose of 25mg 7 days later. During the psychedelic experience, the patients were allowed to "journey" and were mostly uninterrupted. Tranquilizing agents were available as needed that included lorazepam or risperidone in the case of panic attacks or psychotic or agitated behaviors. The participants reported only minimal effects from the psilocybin that peaked at 3 hours and abated by 6 hours. Follow up assessments using QIDS showed decreases for all patients starting at 1week post-dosing with maximum decreases noted at 2 weeks. BDI scores of less than 9 are indicative of remission and scores that were higher than 9 but still showed a 50% decrease from baseline are considered responsive to therapy. In this study 8 of 12 (66%) patients achieved remission at 1 week, and at 3 months, 5 of 12 (42%) of patients achieved sustained remission with two additional patients meeting criteria indicating a response to the therapy. All but one of the participants had a decrease in depressive symptoms at 3 months follow up

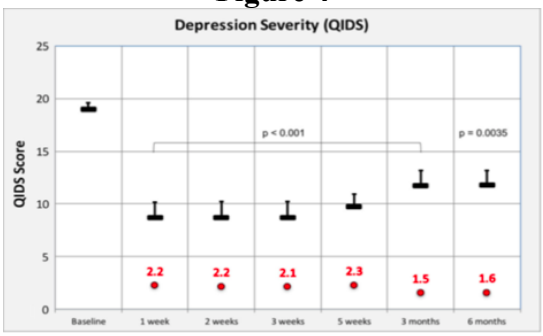
as detailed in **Figure 3.** The main adverse effects associated with psilocybin dosing were transient anxiety, headache, nausea, and confusion at the initial administration and headaches 1-day post-administration that resolved after 1-2 days. There were no residual adverse effects reported[7]. The primary limitations identified in this study were the lack of a control group and a small sample size.

Figure 3



A second study looking at the antidepressant effect of psilocybin was also conducted by Carhart-Harris et al. in 2017 and using a similar research protocol and the same psychometric assessment standards. However, this study had a larger patient population of 20 participants, 12 of which came from the first psilocybin study above and were at the 6 months follow up period. The study included a psychological support component that involved three parts: preparation work, supportive therapy sessions during and after administration, and integration, which involves non-judgmental support after the experience. In this study, 18 out of 20 patients met the criteria for severe or very severe depression, based on a QIDS score >16. The mean number of years of illness was 17, and the median number of medication trials was four. One patient did not complete all of the assessments and was excluded from the final analysis. The results from the two dosage groups of 10mg and 25mg showed that all 19 patients had a statistically significant decrease in their QIDS scores with the maximal effect being seen 5 weeks post-administration, but scores continued to decrease over the 6-month observation period **(Figure 4)**. The BDI also showed improvement in all participants starting at 1-week post-administration, which was maintained at the 6 months follow up, with all the results being statistically significant. Of note, suicide scores also did decrease with 16 of 19 patients scoring 0 on the HAM-D 1-week post-administration. Six patients were started on an antidepressant medication by 3 months, five patients received therapy by the 3 month follow up, and five patients also administered additional psilocybin. All the treatments were well-tolerated, but one patient experienced a transient episode of uncommunicative time during the peak effects of the higher dose, that subsequently resolved without intervention, later during the therapy session. The patient described his experience as "blissful and overwhelming" but failed to complete further assessments[12]. Overall this study showed continued improvement in depressive symptoms 6 months post psilocybin administration. It had similar limitations to the previous study with a small study population and was also an open-label design.

Figure 4



QIDS scores done at baseline and the various times all showed a decrease in scores at all the time frames and all were statistically significant.

In the final study on depressive symptoms, Hendricks et al. conducted a review of participants who had used psilocybin in the past and rated their psychological

distress in the past month (1= yes and 0=no), and suicidal planning or suicide attempt in the last year (1= yes and 0=no, as the primary outcome measures. All participants were contacted via the National Survey on Drug Use and Health from the years of 2008-2012, which had 191,832 total respondents. The participants were separated into four distinct groups: Psilocybin use only (7,550 or 2.47%), Psilocybin and other psychedelics (12,724 or 6.49%), Non-psilocybin psychedelics (6,963 or 4.59%) and no psychedelics (164,595 or 86.42%). Each of the groups were compared to each other. **Table 2** shows that the Psilocybin only group had a significant decrease in both psychological distress and suicidal behaviors when compared to the group with no reported psychedelic use. There was a statistically significant decline in suicidal thinking and suicidal planning categories for the Psilocybin only group when compared to Psilocybin and other psychedelic use groups. When the Psilocybin only group was compared to the non-psilocybin psychedelic use group. the only statistically significant result was that the psilocybin only group had a greater reduction in reported psychological distress. Several categories looking at measures of psychological function had to be excluded due to confounding factors in the no psychedelic use group that heavily skewed the data analysis process[13]. This study highlights the success that psychedelics and specifically psilocybin can have in the treatment of psychological distress and, more importantly, suicidality. These results support future prospective research, which aims to examine these relationships further. One major limitation of this study is the skewed sample size that favors non-psychedelic users, which, as a result, is likely to contain more psychopathology than the other groups. It is reasonable to presume that an increase in psychopathology within a group would make them more likely to experience and report symptoms of psychological distress and suicidality. Another significant issue with this data set is the lack of standardization of psilocybin use, time frame of use recall bias, and the inability to control for potential confounding factors.

Table 2

Table 1

Results of planned contrasts among four groups: Psilocybin Only, Psilocybin & Other Psychedelics, Non-Psilocybin Psychedelics Only, and No Psychedelics

Planned contrasts	Outcome variables			
	Psychological distress OR (95% CI)	Suicidal thinking OR (95% CI)	Suicidal planning OR (95% CI)	Suicide attemp OR (95% CI)
Psilocybin Only vs. No Psychedelics	.70 (.60-.81)†	.76 (.64-.90)**	.54 (.36-.82)**	.58 (.35-.94)*
Psilocybin Only vs. Psilocybin & Other Psychedelics	.89 (.75-1.05)	.80 (.67-.96)*	.59 (.43-.81)**	.75 (.49-1.14)
Psilocybin Only vs. Non-Psilocybin Psychedelics Only	.76 (.64-.90)**	.89 (.72-1.09)	.83 (.54-1.27)	1.06 (.62-1.80)
Psilocybin Only and Psilocybin & Other Psychedelics vs. No Psychedelics	.74 (.65-.84)†	.85 (.75-.96)*	.70 (.49-1.005)β	.66 (.45-.98)*

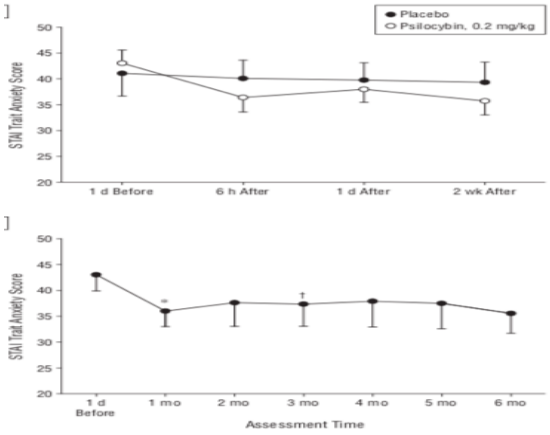
ANXIETY

Psilocybin has also shown potential treatment in anxiety disorders. Generalized anxiety is defined as excessive anxiety or worry that is present most days for at least 6 months with at least 3 of the following physical symptoms: restlessness, fatigue, concentration issues, irritability, muscle tension, and sleep changes[11]. Anxiety can be a symptom of numerous other conditions, including adjustment disorder, acute stress disorder, and anxiety disorder due to a general medical condition.

In 2010 Grob et al. conducted a study examining the use of psilocybin for the treatment of anxiety in patients diagnosed with cancer. The study looked at 12 patients diagnosed with an anxiety disorder, which included generalized anxiety disorder, acute stress disorder, anxiety disorder due to cancer or adjustment disorder diagnosed using the DSM-IV diagnostic criteria. Eleven of the twelve patients were female, and all patients were diagnosed with one of the following types of cancer: breast, colon, ovarian, peritoneal, or salivary. During the study, two patients died due to complications of their cancer, and

another two became too ill to continue to participate in the follow-up process. Exclusion criteria were malignancies involving the CNS, abnormal hepatic or renal function, diabetes, a history of schizophrenia, bipolar or other psychotic disorder, and pre-existing anxiety or affective disorder within 1 year of the cancer diagnosis. This study included a placebo dose of medication in addition to the two doses of psilocybin that were given to the patient several weeks apart. The process was double-blind, and the administration order of the medication was randomly determined for all of the patients. Niacin was chosen as a placebo due to its mild physiological reaction without any psychological effects. Participants were in the treatment room for 6 hours with staff there throughout treatment, staff engaged the patient every hour for assessment but otherwise allowed the patient to experience the effects of the psilocybin undisturbed. Each subject completed the BDI, profile of mood states (POMS), and State-trait anxiety inventory (STAI) before each session and then were re-administered the day after the session, at 2 weeks then monthly for a total of 6 months. A dose of 0.2mg/kg was administered in pill form. The results of this study showed a decrease in the STAI, which was not statistically significant at 6 hours. A sustained, though minimal, decrease in STAI scores was statistically significant at the 1, 3, and 6 months follow up assessments **(Figure 5).** The significance of the STAI score reductions likely represents an overall decrease in stress and anxiety decrease over time[14]. The significant finding of this study was that even small doses of psilocybin can still result in a reduction of anxiety. The limitations of this study were the small sample size, the fact that each patient had late-stage cancer as this limits the generalizability of the population, and the lower dose of psilocybin when compared to other studies that showed higher doses of psilocybin to be more effective in the treatment of affective disorders.

Figure 5

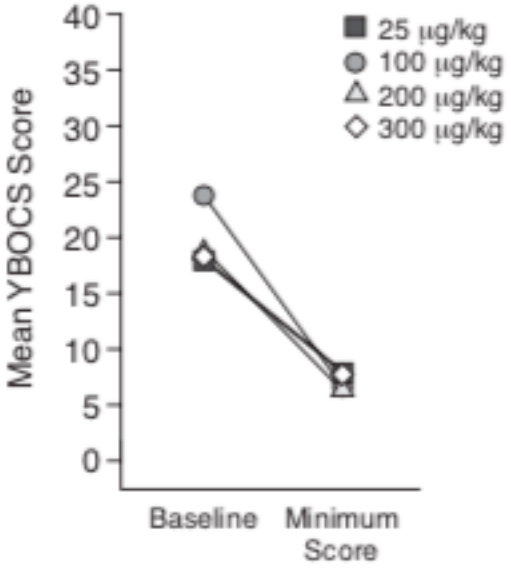


A case report by Wilcox in 2014 examined the effects of psilocybin on Obsessive-Compulsive Disorder (OCD) and found a decrease in symptoms post-administration. This case followed a 38-year-old male with a history of anxiety since childhood that gradually progressed into intrusive and disturbing thoughts, repetitive behaviors with ritualistic aspects, and an excessive degree of worry that occurred about 100 times per day. He previously failed several medications trials, including diazepam, fluoxetine, buspirone, and clomipramine. The patient had also attempted psychotherapy, which was as ineffective as the psychopharmacologic interventions. He decided to consume “magic mushrooms” obtained from a friend and reported that during the psychedelic experience, he had extremely unpleasant feelings and increased anxiety levels. However, over subsequent days, his intrusive thoughts decreased significantly, and this decrease lasted about 3-4 weeks. The patient reported that he consumed approximately 2g of psilocybin and repeated this dose every 3 weeks for 1 year. At the end of that year, the patient was evaluated in the clinic and reported a complete resolution of his OCD symptoms[15]. While this is just a single case

report, the significant response achieved in this patient is encouraging. One other major limitation in this study was the fact that the patient grew his mushrooms, making it difficult to determine the dose and potency of the psilocybin used.

Only one trial has been done that examined the relationship between psilocybin therapy and OCD symptomatology by Moreno et al. in 2006. In this study, 9 participants with DSM-IV diagnosis of OCD with a history of at least one treatment failure while on an SSRI for a minimum of 12 weeks. Treatment failure was defined as a lack of OCD symptom improvement during those 12 weeks. Overall, participants had an average failure of 3.4 medications. Yale-Brown Obsessive-Compulsive (YBOC) scales were obtained, and the ranges were 18-36 with an average score of 24. All participants had only a diagnosis of OCD. The participants received four different dosages during their sessions with increasing doses administered at each subsequent encounter. The doses were 0.025, 0.1, 0.2, and 0.3mg per kg (of note they measured their doses in µg/kg, but for ease of comparison, the doses were converted). All administration days were separated by 1 week, and the participants were able to wear blindfolds and listen to music. The psychedelic experience lasted approximately 8 hours on average. The only adverse effect noted was that one participant had transient hypertension after the ingestion of the 0.2mg/kg dose. Two of the participants dropped out after the first experience due to discomfort with the hospitalization. YBOC scoring was done 24 hours after administration and showed a decrease after all doses, even the very low dose of 0.025mg/kg. **Figure 6** shows the mean YBOCS score and mean minimum score at each dose. An average score of 5-10 on the YBOC was noted post-administration as opposed to the higher score of 20 at baseline. The lowest dose psilocybin did not induce any of the classic psychedelic effects and was meant to act as a control[16]. The significance of this study shows that even low doses of psilocybin are effective at decreasing symptoms of OCD based on validated psychometric questions like the YBOC.

Figure 6



ANXIETY AND DEPRESSION IN TERMINAL ILLNESS

Several studies looked at both depression and anxiety symptoms in terminally ill cancer patients and the effects that psilocybin has on decreasing symptoms associated with these conditions in this population.

The first study was conducted by Griffins et al. in 2016 and followed 51 patients with various cancer diagnoses that were presumed to be terminal. Types of cancer in this group consisted of breast, upper aerodigestive, Gastrointestinal, Genitourinary, and hematological. All of the participants had a DSM-IV diagnosis of chronic adjustment disorder with anxiety (11), chronic adjustment disorder with mixed anxiety and depressed mood (11), dysthymic disorder (5), generalized anxiety disorder (5), Major depressive disorder

(14) or a combination of the aforementioned diagnoses (5). This study was done in a two-session double-blind fashion with low (1-3mg/70kg) versus a high dose (22-30mg/70kg) psilocybin. The doses were administered approximately 5 weeks apart, and the low dose was intended to act as the placebo group. These groups were randomized and assigned to either high or low dose group first.

Assessments were done after enrollment, prior to administration, on both administration days during and at the end of the psychedelic experience, 5 weeks after each session, and 6 months after session two. The sessions were done in a living-room environment, and the patients were encouraged to lie down and use the eye mask while listening to universal music. Of note, the high dose group was decreased to 22mg after 3 of the first participants developed nausea and were discontinued from the study after administration, and the low dose was reduced from 3mg to 1mg after 12 participants had psychedelic effects on the 3mg and the concern was raised about the lack of placebo effect. The primary outcome measures for this study were the GRID-HAMD-17 for depression and HAM-A for anxiety. The results of this study are detailed in **Table 3.** Compared to baseline, there were significant decreases after the administration of the high dose of psilocybin, in both the GRID-HAMD-17 and HAM-A. These results were statistically significant. Although there was no further decrease at the 6 months follow up, the scores continued to remain stable[17]. Overall the primary outcome shows that psilocybin could be useful in the treatment of depression and anxiety in the setting of terminal illness such as cancer.

Table 3

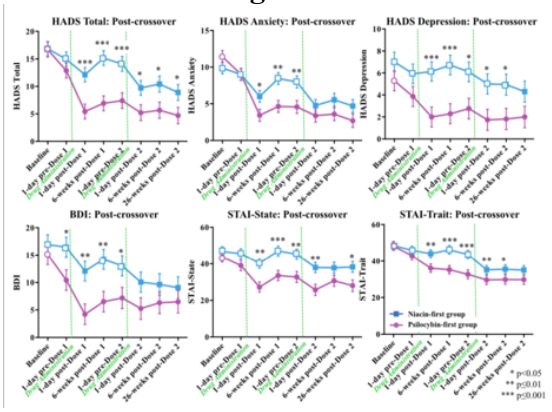
Measure	Group	Assessment time-point			
		Baseline[a]	Post-session 1[b]	Post-session 2[c]	6 months[d]
GRID-HAMD-17 (Depression)	Low-Dose-1st (High-Dose-2nd)	22.32 (0.88)	14.80 (1.45)	6.50 (0.86)***	6.95 (1.24)
	High-Dose-1st (Low-Dose-2nd)	22.84 (0.97)	6.64 (1.04)***	6.52 (1.44)	6.23 (1.30)
HAM-A (Anxiety)	Low-Dose-1st (High-Dose-2nd)	22.88 (0.80)	14.36 (2.11)	6.38 (0.94)***	7.82 (2.12)
	High-Dose-1st (Low-Dose-2nd)	23.52 (1.11)	8.48 (1.01)***	5.25 (1.15)	7.40 (1.12)

*** indicating a p<0.001.

Ross et al. conducted a similar study in 2016 that also examined the effects of psilocybin therapy in patients diagnosed with cancer who were suffering from symptoms of depression and anxiety. The treatment group was administered psilocybin 0.3mg/kg, and the control group was administered niacin 250mg for the reasons previously discussed, all participants received both medications as this was a cross-over study design. The 29 participants were randomized into treatment 1st and treatment 2nd groups in a double-blinded fashion. A unique feature in this study is that each participant underwent a session of psychotherapy during the psychedelic experience. Dose 1 occurred 2-4 weeks after baseline assessments and then the cross-over dose (dose 2) 7 weeks later. Assessments were done at baseline, 1 day before each session, the day of each session (7 hours post-administration), 2 weeks after each session, 6 weeks after each session, and finally 26 weeks after session 2. All of the patients had been diagnosed with an anxiety disorder by DSM-IV criteria, and most had previously failed medications trials that included antidepressants and anxiolytics, but none were on psychotropics at the time of the study. The primary outcome scales used in this study were the Hospital Anxiety and Depression scale (HADS), BDI, and STAI. The results showed significant decreases in the psilocybin group only, shown in **Figure 7.** The effects of psilocybin have a rapid onset which results in a substantial reduction in symptoms associated with depression and anxiety in terminally ill cancer

patients. Additionally, these effects appear to be maintained at long-term follow-up intervals[18].

Figure 7



ADDICTION

Psilocybin has also shown significant potential in the treatment of addiction and substance use disorders, such as alcohol use disorder and tobacco use disorder. Alcohol use disorder defined, per DSM-V, as a "problematic pattern of alcohol use leading to clinically significant symptoms with at least 2 of the following in a 12-month span: Alcohol taken in larger amounts than normally intended, unsuccessful attempts to cut down, a great deal of time is spent in obtaining alcohol or using or recovering, cravings for alcohol, alcohol causing issues with fulfilling major roles in life, continued use despite social or interpersonal problems, important activities given up to use, continued use in dangerous situations, continued use despite recurrent social and interpersonal issues while on alcohol, tolerance, and withdrawal." The severity is stratified by the number of symptoms: mild is 2-3, moderate is 4-5, and severe is 6 or more. Tobacco use disorder and all other substance use disorders use the same criteria listed above[11].

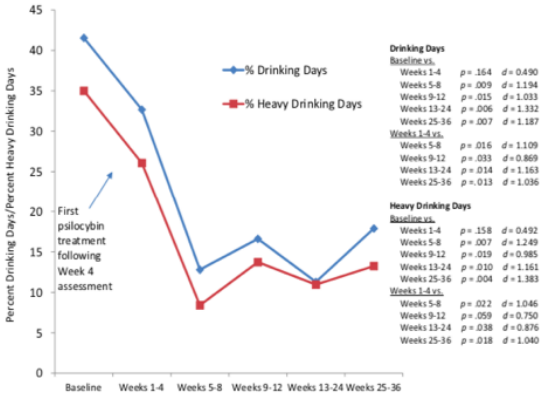
The first study was conducted by Bogenschutz et al. in 2015 and looked at the treatment of alcoholism with psilocybin. In this study, participants were recruited and screened for alcohol dependence based on DSM-IV criteria with at least 2 heaving drinking days per 30 days, and a total of 10 participants were selected for the study. Exclusion criteria included a history of bipolar, schizophrenia, and additional drug dependence. The participants underwent 12 sessions of therapy that included motivational enhancement therapy, a form of motivational interviewing, preparation sessions, and debriefing sessions. Four therapy sessions occurred before the first dose of psilocybin, four sessions after the first dose, and then four sessions after the second dose.

Before both dosing sessions, the participants were required to abstain from alcohol use for 24 hours and were evaluated for signs or symptoms of withdrawal. The treatment rooms were living-room-like and had headphones and eyeshades, and each session lasted 8 hours. The dose of psilocybin administered each time was 0.3mg/kg for the first session and 0.4mg/kg for the second session. Three participants dropped out of the study before the second dose, but two of them completed all of the follow-up assessments and were included in the final analysis. One of the participants received 0.3mg/kg on both the first and second sessions due to having a mystical experience during the initial session. The first dose of psilocybin was administered at week 4 after the aforementioned psychotherapeutic interventions had been completed, and then the second dose was administered following week 8.

The study tracked the number of heavy drinking days, defined as drinking more than 5 drinks in a sitting for men and 4 drinks for women. Additionally, the authors assessed the number of drinking days as defined by the consumption of any alcohol. During weeks 1-4, in which only psychotherapy was given, there were no significant changes in drinking days and heavy drinking days. After the first dose of

psilocybin both, heavy drinking days and total drinking days decreased significantly at all data points when compared to baseline and weeks 1-4, except heaving drinking days in weeks 9-12 compared to weeks 1-4, **Figure 8.** The results are incredibly encouraging, given the significant decrease in alcohol consumption after just one dose of psilocybin[19]. Limitations of this study include the small sample size and a concern about how severe the alcohol dependence/use disorders were given that no patients exhibited withdrawal symptoms after 24 hours of alcohol cessation.

Figure 8

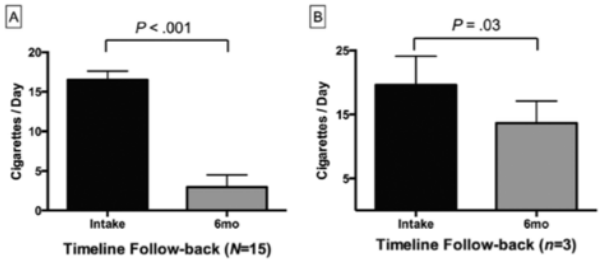


A meta-analysis examining the effects of different serotonergic psychedelics on patients with alcohol use disorder was performed by Garcia-Romeu et al. in 2019. The study design was based on surveys that were sent out requesting participants who had overcome alcohol or drug addiction after using psychedelics. Inclusion criteria were aged 18 years or older, read and write English, retrospectively had a DSM-5 diagnosis of alcohol use disorder, and had classic psychedelic use outside of a medical setting. In total, 343 respondents were included in the meta-analysis. The most common psychedelics used in the population were LSD and psilocybin. About 72% of participants met the criteria for alcohol use disorder, severe with the mean number of DSM-V symptoms being 7.3 and nearly 25.5 drinks per week. The average score on the Alcohol Use Disorders Identification Test - Concise (AUDIT-C) was 8.5 in the year prior to the psychedelic experience. These scores support the notion that the participants were heavy users with significant symptoms. An Alcohol Urge Questionnaire (AUQ) was conducted for cravings in the survey with most of the participants indicating they used "moderate or high" doses of the psychedelic substance and very few had intended to use it as a quitting agent. Nearly all of the participants had reported cessation or significantly reduced their drinking by self-reported number of drinks per week down to 4.3 from 25.5. The AUDIT-C scores decreased to 5.8 from 8.5, and approximately 83% of participants no longer met the criteria for alcohol use disorder. The data showed a significant decrease in AUDIT-C scores with the most significant changes occurring in the higher the pre-AUDIT-C score was[20]. This study strengthens the case that psychedelics and specifically psilocybin should be further investigated as a treatment modality for alcohol use disorder. The major limitations of this study include the fact that all of the data was retrospectively collected, raising the concern for recall bias for both alcohol consumption and the psychedelic dose and agent, which could confound the data significantly. Another limitation was the study advertisement used to recruit implied that psychedelics were the cure, and it is not clear to what degree this caused a selection bias in the responding sample and does not take into account other potential variables that could have contributed to the patients reducing their alcohol intake.

In regard to tobacco use disorders, Johnson et al. in 2014 conducted a 15-week trial to see if psilocybin could be used to decrease tobacco consumption. The study team recruited participants by advertisements and then conducted phone interviews

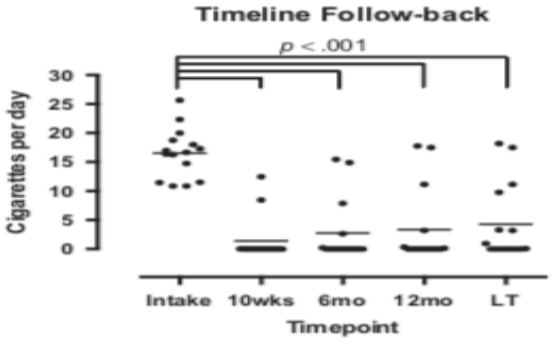
with 15 participants meeting the minimum smoking requirement of 10 cigarettes per day with multiple unsuccessful quitting attempts and the current desire to stop smoking. Exclusion criteria were personal, or family history of a psychotic disorder or bipolar disorder and a history of drug or alcohol dependence based on DSM-IV criteria. Participants underwent four weekly meetings consisting of CBT for smoking cessation in preparation for psilocybin administration with a targeted quit date that was the same as the psilocybin administration, approximately week 5. On that date, participants were given a dose of 20mg/70kg, this dose was repeated at week 7, and an optional higher dose of 30mg/70kg was offered at week 13 for those who requested it. The environment of the room was similar to the other studies detailed above. Smoking markers measured were exhaled Carbon monoxide (CO) (measures smoking over the last 24 hours) and urine cotinine level (measures smoking over the previous 6 days). These markers were obtained at intake, weekly during the intervention, and then at 6 months. Non-smoking status was considered to be a CO of less than 6ppm and a urine cotinine level of less than 200ng/ml. Twelve of the participants completed all three psilocybin sessions, with one of the participants electing the lower dose at session two. At the 6 months follow up assessment, the participants had significant decreases in self-reported number of cigarettes per day, breath CO levels, and urine continue level. Three of the participants reporting smoking at 6 months, but they also had significantly reduced the number of cigarettes per day, as shown in **Figure 9**[21].

Figure 9



The second study was a longer-term follow up on the same 15 participants and was done by Johnson et al. in 2016. The researchers invited participants back at 12 months, and then long term follow up with a mean of 30 months, with all 15 of them participating in the 12-month follow-up and 12 in the long-term follow-up. At 12 months, 10 of the 15 participants reported being smoke-free, and this was confirmed using exhaled CO and urine cotinine testing. At the long-term follow-up 9 of the 12 participants reported and were confirmed to be smoke-free. All of these results at the follow-up time points were statically significant and are detailed in **Figure 10**[22]**.** This data is significant as it shows that both short term and long-term follow-up show substantial decrease in smoking cessation when psilocybin is used in combination with CBT.

Figure 10



CONCLUSIONS

Based on the above articles and reviews examined, it does appear that there is significant evidence that psilocybin has efficacy in treating treatment-resistant depression and anxiety disorders. This efficacy

extends over to the treatment of anxiety and depression in patients with terminal illnesses like cancer. While depression and anxiety disorders compose the large proportions of all psychiatric diagnoses, the treatment-resistant cases are a relatively small number due to the modest success of the standard treatment options. The same cannot be said for substance use disorders like alcohol and tobacco use. The significant potential that psychedelics like psilocybin have shown in the treatment of these conditions is highly encouraging and could be practice-changing in the not too distant future. It would be of great benefit to further examine the benefits that psilocybin can have on treating these different psychiatric disorders with larger sample sizes and longer follow-up.

DISCUSSION

Psychedelics are in a renaissance of psychiatric research, and based on the above studies, it appears that they have efficacy in treating depressive symptoms, anxiety disorders, and substance use disorders. The benefits of psychedelics and psilocybin in particular far outweigh the risks when these agents are used in a therapeutic environment under standardized protocols. With careful screening and a safe and supportive environment, psychedelics like psilocybin have the potential to revolutionize the landscape for the treatment of chronic refractory or resistant conditions that currently only have limited options for management. As discussed in a review article by Gardner et al. in 2019, the area of psychedelics is an emerging field, and much more research is needed. The legal classifications need to be re-evaluated as it is clear that psychedelics do have a clear medical benefit and are also not addictive or habit-forming. The negative social connotations associated with psychedelics have even begun to shift in a positive direction making the discussion about these agents more straightforward and honest. Further change will be required before psychedelics can be fully incorporated into a standard clinical practice, but based on the current research findings, it is reasonable to believe that these agents will be of substantial benefit when that day finally arrives[23].

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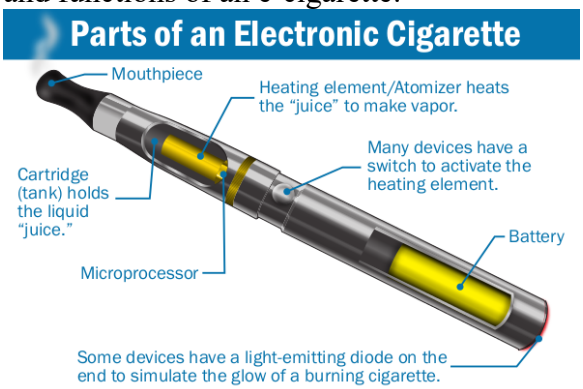
Beyond Vaping: Psilocybin for the Treatment of Tobacco Use Disorder

Tyler R. Kjorvestad, M.D.

Ceman's [1] review, in this issue, examines the potential uses of psilocybin with associated psychotherapy for the treatment of numerous conditions. One such condition is tobacco use disorder and, more specifically, cigarette smoking. The Centers for Disease Control and Prevention (CDC) estimated in 2017 that "14.0% (34.3 million) of U.S. adults were current cigarette smokers. Of these, 75.0% smoked every day [2]". The CDC also notes that cigarette smoking is more common in individuals of lower socioeconomic status, with more comorbid medical and psychiatric conditions. They state that "1 in 4 (or 25%) of adults in the U.S. have some form of mental illness or substance use disorder, and these adults consume almost 40% of all cigarettes smoked by adults overall [3,4,]". Cigarette smoking is responsible for the death of "more than 480,000 each year. In addition, smoking-related illness in the United States costs more than $300 billion a year, including nearly $170 billion in direct medical care for adults and $156 billion in lost productivity [5,6]". Any treatment modality that can reduce or mitigate the costs associated with cigarette smoking morbidity and mortality should strongly be considered, if not wholeheartedly embraced.

Initially, this novel treatment modality was thought to have arrived in the form of electronic cigarettes (e-cigarettes), which allow users to inhale nicotine separate from tobacco in a process similar to smoking which is commonly referred to as "vaping." There is a high level of heterogeneity among e-cigarettes, but in general, they are defined as "battery-powered devices which simulate tobacco smoking by producing a heated vapor that resembles smoke." The liquid solution is heated by an electric heating element, typically referred to as an atomizer or cartomizer, until the liquid transitions to a vaper [7]. The first known e-cigarette was patented in 2003 and first made available for sale in 2007 [7]. As of 2014, there were over 450 different brands and over 7,700 different flavors available for purchase [7]. Propylene glycol and vegetable glycerin are often added to the nicotine and flavoring to increase flavor and vapor production, respectively [7]. Figure 1 [7] details the design, associated parts, and functions of an e-cigarette:



The Federal Drug Administration (FDA) was given authority over tobacco products starting in 2009, but at that time the FDA deemed e-cigarettes to be a "drug delivery device" which meant that all e-cigarettes were subject to the regulations established under the Food, Drug, and Cosmetic Act of 1938 [8]. This designation meant that e-cigarette producers had to meet additional standards to bring their product to the market compared to if e-cigarettes had been classified as a "tobacco product." Manufacturers of e-cigarettes sued the FDA and won, meaning that e-cigarettes were classified as a tobacco product,

and the FDA released a revised ruling in 2016 [9]. While this ruling allowed e-cigarettes to be sold like cigarettes, it had the unintended consequence of preventing e-cigarettes from being marketed as a smoking cessation device. According to FDA regulations, e-cigarettes were essentially no different from a cigarette insofar as they were a nicotine delivery system [10]. This decision created a perverse incentive and resulted in some e-cigarette companies creating a marketing campaign that, at the very least, appeared, if this wasn't the explicit intent, to target teens and young adults [11]. Likely in part as a result of these campaigns, the largest demographic of individuals who report vaping is 18-24-year-olds, [12] and the rate of high school seniors who "reported smoking in the 30 days prior" was 20.9% in 2018 almost double the rate from 2017 [13]. These factors led to a growing concern among parents and regulators about vaping in this population, and this was before the epidemic of vaping associated lung injuries (VALI) that began to occur in 2019.

VALI has become an extremely contentious topic within the media, who have done an absymal job of reporting the facts surrounding these injuries. According to the latest information from the CDC as of November 2019, there have been "2,172 EVALI cases to the CDC, including 42 (1.9%) EVALI-associated deaths" with 77% of these patients being under the age of 35 [14]. Additionally, 83% of hospitalized patients and 84% of individuals not hospitalized for VALI reported the use of THC-containing products [14] with examination of lung tissue from 29 patients from 10 states showing that all tissue samples contained vitamin E acetate oil. The finding of vitamin E acetate oil is extremely significant since the initial coverage of VALI strongly implicated nicotine-containing e-cigarettes and lead to discussions about additional regulation and even a total ban of e-cigarettes. A ban would be a completely unjustified overreaction if it were to occur. E-cigarettes have only been on the market for just over a decade before the start of this epidemic, which seems to be overwhelmingly linked to the inappropriate use of mostly unregulated THC-containing compounds, there has been little to no evidence that nicotine only solutions can cause VALI. These results are true not only in the United States but also in the United Kingdom and other countries that have been selling e-cigarettes for roughly the same period.

The benefits of properly used e-cigarettes far outweigh the risks of use, especially when compared to traditional cigarettes. Cigarettes contain over 7000 different compounds, over 60 of which are known to be carcinogenic [15]. By contrast, the additives in e-cigarettes, such as propylene glycol, vegetable glycerin, and associated flavorings, are generally well-tolerated and used in the production of numerous edible compounds. Cigarettes and e-cigarettes both pose a fire hazard, whether through combustion with cigarettes or mechanical failures with the vaporizer or heating element in e-cigarettes. Additionally, both can result in burns to the skin and irritation of the mucosa when inhaling. Tobacco products and e-cigarettes both contain nicotine which is a highly addictive substance that has been partially implicated as a causative agent in an extensive number of medical conditions but is also touted by proponents as aiding with attention and improving cognition. Evidence supporting the majority of these claims, both for and against, remains extremely limited, and most studies have not adequately demonstrated an association between pure nicotine use and either positive or negative outcomes [16]. Despite all of these potential risks, the evidence that e-cigarettes are safer than traditional cigarette

use is clear and indisputable. In 2015 Public Health England concluded that e-cigarettes were 95% less harmful than smoking [17]. Further research has shown that e-cigarettes reduce exposure to particulate matter, carbon monoxide, and other toxic and potentially harmful constituents [18].

While e-cigarettes are a viable and preferable alternative to traditional tobacco use, their effectiveness in the treatment of tobacco use disorders has only limited evidence. This lack of evidence is due in large part to the fact that e-cigarettes cannot be marketed as smoking cessation devices given the FDA's previously mentioned designation as a tobacco product, thus limiting potential research investigations. However, a 2018 randomized control trial (RCT) looking at smoking cessation rates compared an e-cigarette group to a nicotine replacement therapy (NRT) group and found that at one year the e-cigarette group had an abstinence rate of 18% compared to 9.9% for the NRT group [19]. However, there have been no studies yet comparing e-cigarettes to other tobacco use disorder medications such as bupropion or varenicline.

Pharmacotherapy for tobacco use disorders is relatively limited, with strong evidence only supporting the use of varenicline, bupropion, and NRT in combination with smoking cessation counseling. Varenicline is the most effective monotherapy for tobacco use disorders, with a 1-year abstinence rate of 22-23% [20]. Bupropion has a 1-year abstinence rate of 15-16% [20], and NRT using multiple routes of administration has a 1-year abstinence rate of 7% [21]. A 2017 large multicenter randomized, placebo-controlled trial looked at the efficacy of tobacco use disorder therapies versus placebo for abstinence rates over 24 weeks and found that varenicline was 2.94 times more effective than the placebo. Bupropion and NRT were 1.96 and 1.86 times more effective than placebo, respectively [22]. All of the medications have substantial relapse rates, with some studies showing 12-24-week abstinence rates to be approximately twice as high as the 1-year rates. It should also be noted that mixed evidence exists for the use of combination therapy of varenicline and bupropion as a potentially superior therapy compared to either as monotherapy based on 1-year abstinence rates [23].

While there is only limited data on the use of e-cigarettes for the long term treatment of tobacco use disorders, it is reasonable to hypothesize that their efficacy would likely be similar to, and possibly superior to, bupropion insofar as 1-year abstinence rates are concerned. Rates could be higher, as other studies have reported that 30.4% of smokers who transitioned to e-cigarettes quit smoking entirely [12], but further research will be needed to elucidate these results fully. Another potential area of focus is determining the best method of transitioning to e-cigarettes, as 54.6% of those who vape also use traditional cigarettes. Conversely, there is a roughly 15% subset of the e-cigarette user population, [12] who were never tobacco users. While the evidence is clear that e-cigarettes are safer than traditional cigarettes, their use should not be encouraged in individuals who are not current tobacco users due to the limited data on the long-term use of these products.

Furthermore, the lack of evidence on the long-term use of pure nicotine should cause additional pause, especially given that e-cigarettes can contain up to 5% [24] nicotine compared to the 1-2% [25] seen in traditional cigarettes. The risks of e-cigarettes have not been conclusively stratified and also offer a mechanism to misuse or abuse compounds containing THC and other additives resulting in life-threatening complications such as VALI. The lack of superior efficacy, limited long term data, and safety concerns surrounding e-

cigarettes necessitates further research into alternative therapeutic agents for the treatment of tobacco use disorders. One such agent is psilocybin, which has shown potential in the treatment of numerous conditions and specifically smoking cessation.

In a small-scale study, 15 patients were given two to three moderate doses of psilocybin over the span of eight weeks in addition to evidence-based cognitive-behavioral therapy (CBT) for smoking cessation. At six months, 80% of the treatment group was abstinent from smoking, with rates decreasing to 66% at one year and 60% at 30 months [26]. These results are encouraging for the long-term treatment of tobacco use disorders insofar as psilocybin offers numerous advantages compared to standard therapy. Psilocybin, when administered in a therapeutic environment under appropriate protocols, is an extremely safe and well-tolerated medication. It, like other classical psychedelics, is nonaddictive, has no known overdose potential, and repeated administration within a short time causes rapid tachyphylaxis at the 5-HT_{2A} receptor site [27]. The side effects associated with the use of psilocybin and other psychedelics are generally limited to the duration of the experience. They can include anxiety, panic attacks, nausea, vomiting, diaphoresis, and depersonalization, which can be minimized when taken in therapeutic environments with trained professionals. One significant risk is the exacerbation of underlying severe psychiatric illnesses such as schizophrenia and bipolar disorder, though no evidence suggests that these agents cause severe psychiatric conditions, and long-term data actually suggests that psychedelic use is linked with better psychological health [27]. Rare risks include the potential for vasospasm, adverse drug-drug interactions when used with other psychiatric medications such as selective serotonin reuptake inhibitors, and long-term side effects like Hallucinogen Persisting Perception Disorder [27]. The incidence of all of these risks can be reduced by adequately screening patients with corresponding risk factors and excluding those individuals from therapy or more thoroughly counseling them on the potential risks. Tobacco users are already at a higher risk of cardiovascular disease and, therefore, should be counseled on the risks before therapy.

The implications of psilocybin for the treatment of tobacco use disorders could be substantial not only from a population health perspective but also from a healthcare economic standpoint. Even assuming a regression toward the mean and conservative estimates, the benefits of a medication that could hypothetically result in a 40-50% 1-year abstinence rate is still approximately twice as effective as the best current pharmacotherapy. The potential cost savings from this level of intervention would be substantial for direct healthcare expenditures. From a patient's perspective, the cost-benefit ratio would significantly favor psilocybin assisted psychotherapy over the current standard of care. Psilocybin eliminates the problems associated with daily medication compliance and the side effects associated with prolonged use of psychotherapeutic medications. Additionally, it has a more favorable pharmacologic profile and shorter total duration of therapy. Lastly, the likely therapeutic effects on other psychiatric conditions is an added benefit. The positive outcomes from small scale studies, prospective economical cost savings due to improved public health standards, and overall favorable safety profile could make psilocybin a revolutionary treatment. It is imperative that more research is done to investigate the use of psilocybin assisted psychotherapy for the treatment of tobacco use disorders.

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Ayahuasca and Treatment of Post-Traumatic Stress Disorder: A Case Report

Anthony Ceman, M.D.

Post-traumatic stress disorder (PTSD) is a psychiatric disorder that affects about 8% of the population in the United States[1]. Conventional treatments for PTSD are a category of medications commonly referred to as antidepressants (selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors) along with psychotherapy. Only two of these medications have received Federal Drug Administration (FDA) approval for PTSD treatment, Sertraline, and Paroxetine[2]. Current evidence is emerging for the treatment of PTSD symptoms with psychedelic substances, one of which is 3,4-Methylenedioxymethamphetamin (MDMA), with it recently receiving a breakthrough therapy designation from the FDA[2]. This report describes the case of a male United States military veteran who suffers from PTSD symptoms related to both military experiences and childhood trauma and had resolution of those symptoms after administration of Ayahuasca every 6 months under the guidance of a Shaman in Peru. This case serves to provide evidence for the use of Ayahuasca in the treatment of PTSD.

CASE REPORT

Mr. W is a 53-year-old male patient with a diagnosis of PTSD who entered the military at age 18 and had a 20-year career in the United States Army. In his long career, he had several combat tours and was diagnosed with PTSD upon return to civilian status. Symptoms that contributed to this diagnosis included hypervigilance, nightmares, flashbacks, and avoidance of public and social situations. He also had been the subject of childhood trauma that he did not recall until he his PTSD symptoms, from his military experience, began to occur. These symptoms were extremely bothersome to him and subsequently caused him to experience depressive symptoms and at times, suicidal thoughts. His management at the Veterans Administration consisted of numerous different medication trials, including Gabapentin, Xanax, Tegretol, Valium, Prozac, Prazosin, Buspar, Clonazepam, Nortriptyline, Doxepin, Zoloft, and Temazepam. He reported that he had many side effects on these medications, and all were mostly ineffective in treating his PTSD symptoms. He noted that after trying several different medications, he began to have worsened suicidal thoughts and grew more frustrated with his care. He also had been through numerous therapies over the years and did find some of the techniques helpful. However, there was a limit to the amount of improvement in symptoms of PTSD that he had noticed. Even after therapy, he still found it challenging to socialize due to his overall uneasiness in public places, and he continued to have almost nightly nightmares that resulted in mood changes, often including irritability and depressive symptoms.

the late 2000s, he started to explore different religions and eventually identified as a Buddhist and in accordance with Buddhist culture, he went on a spiritual retreat. His retreat occurred in South America. He partook in a religious ceremony that involved the ingestion of Ayahuasca under the supervision of a Shaman. The entire process lasted 8 hours in what he described as a “religious experience.” He states that guided meditation was incorporated into the psychedelic experience, which allowed him to "process" some of his past traumas.

Following the first experience in 2013 he returned home and noticed that his PTSD symptoms had entirely resolved. He felt more comfortable in social situations with a decreased level of hypervigilance, and his nightmares had completely resolved. He continued to practice meditation and Buddhism during this time but had stopped taking any psychotropics by the mid-2000s and had also discontinued psychotherapy around the same time.

He reported the total resolution of PTSD symptoms for about 6-8 months following the administration of the Ayahuasca with recurrence of symptoms shortly after this period. He began to notice increased uneasiness associated with being in public places and return of the nightmares started but to a significantly lesser degree than in the past. Shortly after the return of these symptoms, he went back to Peru for another Ayahuasca experience under the guidance of a Shaman and underwent the same religious ritual and again had complete resolution of his PTSD symptoms.

He has continued to return to Peru for repeat sessions every 6 months and has continued to have resolution of his PTSD symptoms. He states that his life has drastically changed as a result. He is now more comfortable in public places, can keep a full-time job in IT, and has started to form more meaningful relationships that he was unable to do previously as a consequence of his PTSD symptoms. He also has not had any suicidal thoughts in several years and denies any depression or anxiety symptoms during that same period as well, at the time of the interview. He attributes his success and resolution of these symptoms directly to the Ayahuasca and stated he does not know if he would be alive if it had not been for his discovery of Ayahuasca and the Shaman in Peru.

DISCUSSION

A literature review with search terms of Ayahuasca and PTSD reveals one study that hypothesizes that Ayahuasca could assist with PTSD symptoms given its Sigma-1 receptor and MAOI activity. Through this process, it is easier to "retrieve" the traumatic memories and process them[3]. There are emerging studies done with Ayahuasca and treatment-resistant depression[4] and suicidality[5], but no additional studies done on Ayahuasca and the treatment of PTSD symptoms. This case report can add to the literature on Ayahuasca and psychedelic substance use in the treatment of PTSD symptoms. Mr. W found it easier to process the traumas of his past under the Shaman guided therapy assisted with Ayahuasca, which lead to improvement in PTSD symptoms and significant improvement in quality of life after the resolution of these symptoms.

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