Article

LSD: A Comprehensive Review

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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 non-toxic 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, pan-neurosis, 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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