Long-Term Effects of Lysergic Acid Diethylamide (LSD) Use and Potential Medicinal Uses

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Introduction

Lysergic Acid Diethylamide (LSD) is a chemical compound that is commonly used as a recreational, psychedelic drug for its hallucinogenic effects. It was created in 1938 in a lab by Albert Hofmann in an unsuccessful attempt to find a blood stimulant, but once the hallucinogenic effects were discovered, the drug was distributed to psychiatrists around the world to find medical uses for the drug, but this was unsuccessful as well. There has been extensive previous research into the connections between LSD use and mental illness, specifically schizophrenia. Studies of LSD users have shown that the use of the drug and the onset of mental illness are not interrelated, but that LSD users actually experience mental illness at a lower rate (Krebs 2013). Some LSD users may experience Hallucinogen Persisting Perception Disorder (HPPD) or persistent psychosis in the long-term (NIDA 2015). The symptoms of HPPD have not been found to be adverse to those affected, but they can be reversed with the use of monoamine oxidase inhibitors (Bonson 1995). To date, most review literature limits psychedelics to being illicit drugs of abuse rather than having value as future pharmacotherapies (Szabo 2015). The use of LSD for psychotherapy has been explored in past studies, but, more currently, research is being done for the use of LSD as an immunotherapy and to treat mental illnesses. This paper explores LSD as a compound, its mechanism, its effects, the long-term risks associated with use and its connection to mental illness and will shed light on new research that poses LSD as viable for medical use.

LSD Compound and Mechanism

LSD is a semisynthetic derivative of the fungus Claviceps purpurea, more commonly known as ergot (NCBI, 2016). Its molecular formula is C20H25N3O and has a molecular weight of 232.432 g/mol. It is a colorless, odorless and tasteless molecule that is typically in the form of prismatic crystals (NCBI, 2016), but when used recreationally, it most commonly comes in liquid form absorbed onto sheets of paper called tabs (Dutta, 2012). Although oral ingestion is the most commonly used route of administration, it can also be injected, inhaled or transdermally applied (NHTSA, 2012). When ingested, the effects of the drug become apparent in about thirty minutes and last for eight to twelve hours, or more (NCBI, 2016). The drug is water-soluble and decomposes in light and at high temperatures (NCBI, 2016).

LSD is also classified as a serotonergic hallucinogen, meaning the neurotransmitter serotonin (5-HT) is highly involved in its mechanism of action. LSD structurally resembles serotonin, which is an inhibitory neurotransmitter. Serotonin does not directly stimulate the brain but is essential for regulating mood and balancing excessive excitatory neurotransmitter firing in the brain. Serotonin has been found to be connected to many different types of behaviors in humans, including appetitive, emotional, motor, cognitive and autonomic behaviors (Frazer, 1999). Depletion of serotonin can occur over time with the long-term use of stimulant medications and caffeine. Low levels of serotonin have been associated with major depressive
disorder (MDD) and can negatively affect social functioning (Hogenelst, 2015).

LSD is known to interact with the serotonin pathway by binding and activating the 5-hydroxytryptamine sub-type 2A (5-HT2A) receptor. Activation of the 5-HT2A receptor is a common characteristic of serotonergic hallucinogens (Halberstaldt, 2015). This is the primary site for hallucinogen action to create perceptual disturbances in an LSD trip (Halberstaldt, 2015). In human studies, it was shown that there was a strong correlation ($r = 0.90-0.97$) between affinity to the receptor and human hallucinogen potency (Halberstaldt, 2015), which implicates 5-HT2A activation for being the primary receptor responsible for the effects of hallucinogens. Animal studies have also tested drug discrimination of hallucinogens to test the role of the receptor in LSD use. Rats were taught to discriminate between LSD and saline based on psychological effects then were given 5-HT2 antagonists, which led to them losing the ability to discriminate between the LSD and saline (Frederickson, 1998). LSD was also found to have a higher affinity for 5-HT receptors than serotonin, but at lower potencies, which meant that although LSD molecules are more likely to bind to the receptors, they are less likely to have an effect than serotonin molecules.

Three theories for the mechanism of LSD are then proposed. The first poses LSD as a serotonin antagonist that blocks 5-HT receptors and blocks serotonin from having its normal effect (Fredrickson, 1998). This theory was supported by an experiment that paired the administration of antagonists with LSD with no resultant changes in the effects of LSD. Problems with this theory are the excitatory effects associated with LSD intoxication that lead to an increase in neural activity because serotonin is an inhibitory neurotransmitter, which would result in a decrease in neural activity after the introduction of antagonists. In the next theory, LSD is hypothesized to be an agonist rather than an antagonist. This theory is supported by an experiment in which rats lost their ability to differentiate between LSD and saline after the administration of 5-HT2 antagonists. In that experiment, it was also found that LSD had a higher affinity for 5-HT receptors than serotonin did but at lower potencies, as mentioned before. The conclusion of this theory is that LSD may appear to be an antagonist even though it is by definition an agonist. In the last theory, an agonist/antagonist relationship between 5-HT1 and 5-HT2 is hypothesized. This theory is a combination of the first two theories and proposes that substances that are agonistic to 5-HT1 receptors are antagonistic to 5-HT2 receptors, causing serotonin activity to be enhanced at 5-HT1 receptors and blocking the 5-H52 receptors from serotonin activation (Frederickson, 1998).

**LSD Effects**

LSD is classified as a hallucinogen because of its capability to induce illusions, hallucinations, paranoid ideations, and alterations of mood and thinking that are not experienced otherwise. Effects upon the onset of the drug include intense changes in perception, mood and thoughts, as well as hallucinations that mark the loss of sense of reality through the distortion of visual, spatial and temporal perception (Beck 2013). Feelings of euphoria are typically observed, but other feelings are also heightened. Adverse effects of the drug include anxiety, anorexia, ataxia, and pupillary dilations (Beck 2013). An adverse effect that has been specifically studied is the prolongation of the effects of LSD post-use, when the user no longer has the drug in their system, and this is commonly referred to as Hallucination Persisting 2
Perception Disorder (HPPD), which will be discussed more fully in the long-term effects of LSD use.

Somatic effects LSD users feel can include mydriasis, hyperglycemia, hyperthermia, piloerection, vomiting, lachrymation, hypotension, brachycardia and fluctuations in respiratory effects based on dosage (Darke, 1997). Psychological effects include hallucinations, depersonalization, euphoria, megalomania, reduced defenses, being in a schizophrenic-like state and, in some cases, reliving repressed memories. Cognitive effects include disturbed thought processes, difficulty in thought expression, impairment in reasoning, and impairment of memory, especially in the integration of short term-memory to long-term memory (Darke, 1997). Perceptual changes that may occur include increased stimulus from the environment, changes in shapes and colors of objects in the environment, synesthesia, and disturbed perception of time (Darke, 1997).

**Long-Term Use Effects**

Because of the production of similarity of hallucinations that LSD intoxication to those that schizophrenia patients may experience, there is a misconception that LSD use will result in a schizophrenia diagnosis or trigger schizophrenia. Studies of patients who have either used LSD, have schizophrenia, or both have schizophrenia and have used LSD (Lev-ran, 2014) have been used to refute these theories. Although the drug may not induce schizophrenia, there are long term effects that some users may feel, whether they were one-time LSD users or after prolonged use of the drug. Long-term effects of LSD use include Hallucinogen Persisting Perception Disorder (HPPD) and persistent psychosis. HPPD is characterized by hallucinations, visual disturbances and other symptoms that may be mistaken for being associated with a neurological disorder (NIDA, 2015). Persistent psychosis manifests in the form of visual disturbances, disorganized thinking, paranoia, and mood disturbances (NIDA, 2015). Various studies of HPPD in users have been done over time, but there are few to no studies that reinforce a relationship between LSD use and persisting psychosis that the National Institute of Drug Abuse describes as a long-term effect of hallucinogen use.

The prevalence of HPPD in LSD users is suspected to be higher than clinical studies suggest. In a study in the Netherlands followed an artist who had HPPD (Neven, 2014). The study found that the artist experienced synesthesias, even two years after stopping LSD use. A synesthesia is the involuntary or automatic sensation of a sensory modality that occurs when another sensory modality is stimulated (Afra, 2015). The artist experienced hallucinations regularly triggered by olfactory, visual, and auditory stimuli (Neven, 2014). The artist also experienced olfactory and auditory synesthesia, but instances of such hallucinations were not described in HPPD before this study.

More recently, the first case of Alice in Wonderland Syndrome (AIWS) associated with LSD use was reported. Alice in Wonderland Syndrome (AIWS), also known as Todd’s Syndrome, is an HPPD that is characterized by: macropia, micropsia, pelopsia, and teleopsia (Lerner 2015), which are neurological conditions that affect human visual perception by creating the illusion that things are: bigger, smaller, closer, or further, respectively, than they actually are. In most cases, the symptoms associated with AIWS do not cause major functional impairment in the user. The case study reported that the symptoms in the patient were “interesting, benign,
Reversing the Effects of LSD

Although there are some long-term effects associated with LSD that can be risks to users, studies have been done to determine whether or not the symptoms of HPPD can be reversed. An experiment was conducted testing monoamine oxidase inhibitors, antidepressants and lithium for potential use in reversing the long-term effects of LSD use (Bonson, 1995). This study found that the effects of LSD could be reversed with the chronic administration of monoamine oxidase inhibitors, but that the use of antidepressants was associated with the heightening the effects of LSD. This poses an important solution for those that fear long-term effects that may inhibit a user’s lifestyle. This is also important for treating those that experience HPPD and want to stop their persistent hallucinations (Bonson, 1996).

This study also addresses the risk that users could be prescribed antidepressants that will heighten their hallucinations because of being misdiagnosed due to the HPPD’s symptoms appearing similar to that of mood and neurological disorders (i.e. major depressive disorder or bipolar disorder). The paper suggests that psychiatrists need to be cautious when diagnosing these mood and neurological disorders in patients who have a history of LSD use. A different study also reported findings that antidepressants administered to youth with LSD flashback syndrome, which can now be identified as HPPD, exacerbated the effects of the disorder (Markel, 1994).

In Lerner’s study of a patient who experienced AWIS post-LSD use, the study concluded that the long-term effects were harmless and reversible. In the study, their patient refused chemical pharmacological treatments for the AWIS symptoms and opted for a psychiatric follow-up, instead. After a year, the patient reported that all visual disturbances had disappeared (Lerner, 2015).

LSD and Mental Illness

As aforementioned, there have been concerns about the connection of LSD use and developing schizophrenia. More recent research has found that the use of LSD does not initiate schizophrenia, despite its production of schizophrenic behaviors during intoxication and possible HPPD, which can be mistaken for schizophrenia. In a specific study, research characterizing the differences between HPPD and schizophrenia was done and patients with either schizophrenia, HPPD, or both schizophrenia and HPPD were clinically assessed and completed multiple questionnaires regarding their hallucinations (Lev-Ran, 2014). The study found that 75% of patients with both HPPD and schizophrenia were able to distinguish the precursory cues before visual distortion as a result of their HPPD from those of a schizophrenia-related hallucination. It was also found that 67% of those with both HPPD and schizophrenia could distinguish between their HPPD-related perceptual disturbances from those associated with their schizophrenia. The study concluded that there is little known about the co-occurrence of HPPD and schizophrenia, but that further research is essential to understanding the clinical implications of the co-occurrence of the two disorders (Lev-Ran, 2014). Clinical implications most relevant to this paper are the misdiagnosis of schizophrenia in those who actually have HPPD. These patients may be prescribed drugs that will enhance their perceptual disturbances rather than reducing
them because of their misdiagnosis.

The associations between the long-term use of psychedelics and mental health were evaluated in a population study (Krebs, 2013). In the study, mental health indicators from the past year, lifetime use of LSD, psilocybin, mescaline and peyote, and past year use of LSD were measured and the association between those variables were calculated. The association between mental health indicators and subgroup categories such as sex and age were also calculated. Before adjusting for confounding factors, psychedelic users had higher rates of all indicators being measured in mental health problems. In the eight disorders the study was measuring, they found no statistical significance from “no associations” due to psychedelic use. The study even found that there were weak associations between lifetime use of any psychedelic and lower rate of mental health problems and between lifetime use of specific psychedelic drugs, including LSD, and lower rates of mental health problems. The study concluded that their results “might reflect beneficial effects of psychedelic use” (Krebs, 2013) and that their results were consistent with the assessment of drug education programs in the UN, EU, US and UK that do not conclude that psychedelics cause lasting anxiety, depression or psychosis in users (Krebs, 2013).

**Medicinal and Clinical Uses**

The long-term risks associated with LSD use have been discussed, but the safety of the immediate effects of LSD during intoxication are also important to evaluate when considering its use as a therapy. The ability of LSD to cause schizophrenic-like actions and perceptual disturbances may lead to a “bad trip,” which can potentially be dangerous to the mental and physical well-being of the user. One study evaluated the safety of using LSD as a therapy and concluded that if used in a supervised, medical setting, using LSD can be a safe and effective therapy option (Gasser, 2014). The study did call for more and larger studies than their own to further explore any risks associated with the therapeutic administration of LSD.

LSD has proven to be important to clinical research for discovering more about schizophrenia. The similarity between the effects associated with LSD intoxication and schizophrenia symptoms make the drug useful in considering the mechanism of schizophrenia (Martin, 2014). Modulating the positive effects of schizophrenia using LSD has also helped researchers to find linkages between the 5-HT receptors and schizophrenia mechanisms (Halberstadt, 2013). The efficacy of LSD as a model for schizophrenic effects poses the possibility of finding therapeutic agents to treat schizophrenia. The use of LSD, psilocybin and DMT via stimulation of the 5-HT2A receptor have also been proposed as potential therapies to suppress schizophrenia (Halberstadt, 2013).

The recent association established between the 5-HT receptors and psychedelics have sparked renewed interest in the use of LSD and other psychedelics as immunotherapies. Sbazo calls this the “biomedical Renaissance of psychedelic research,” which they date to have started in the early 2000s (Sbazo, 2015). It is understood by the vast amount of research that the mechanism of action of LSD and other psychedelics begin by triggering neurotransmitter receptors in the brain, which creates altered cognition and perception in the user. The immune and nervous systems had not been vastly studied in relation to each other until more recently in research, but it is now understood that immune cells have neuroreceptors associated with them.
The 5-HT1 and 5-HT2 receptors have a high expression profile in the lymphoid tissues of mammals and are associated with different immunological processes, including anti-tumor and anti-viral immune responses (Sbazo, 2015). Immune homeostasis is also regulated by neuroendocrine regulation of inflammation that happens through serotonin (Sbazo, 2015). The ability of psychedelics to enhance immune response or inhibit functions related to inflammation pose psychedelics as possible remedies to treat diseases with chronic inflammatory etiology and pathology, including atherosclerosis, rheumatoid arthritis, type 1 diabetes, multiple sclerosis, schizophrenia, Alzheimer’s disease and depression (Szabo, 2015).

In the Journal of Cancer Research and Therapeutics, Dutta discusses death being the most repressed consciousness as humans. After the 1970’s, the thought that psychedelics could be used for psychedelic psychotherapy in the terminally ill was abandoned by medical practitioners. Dutta does not suggest that LSD and other psychedelics will cure the fear associated with inevitable death, but proposes that the use of psychedelics to work through existential fears and reduce anxiety associated with death consciousness (Dutta, 2012). In a double-blind study, reductions in trait anxiety and state anxiety, measured using the State-Trait Anxiety Inventory, were sustained for at least 12 months after administration of LSD (Gasser, 2014). The study was addressing the state anxiety, pain and suffering associated with existential threats from shortened life expectancies upon being diagnosed with life-threatening illnesses. The result found that the decreased anxiety, quantified by the STAI scores, were more dramatic after their second session of LSD administration, suggesting that at least two sessions are necessary for the reduced anxiety effects (Gasser, 2014). The study proposes that longer treatments period in which higher dosages of LSD are administered in more sessions as a way to reduce anxiety in the terminally ill.

**Discussion and Conclusions**

The use of LSD, both recreationally and medicinally, has risks associated with it, but potential for its use are too vast to dismiss it as an illicit drug. The safety of LSD use in medical environments has been studied and has thus far proven to be safe, when under proper supervision. Further studies are necessary to determine whether certain genes could be triggered by LSD use so that people who choose to use LSD either recreationally and medicinally can make informed decisions about taking the drug.

Practitioners should be wary when diagnosing their patients with psychiatric disorders because of the ability of HPPD to manifest similarly to some disorders. While HPPD may be induced by LSD use, the symptoms are harmless in most cases. The effects of HPPD can be reversed with the administration of monoamine oxidase inhibitors. More clinical trials are necessary for the administration of this treatment to HPPD patients on a larger scale. The criteria for distinguishing between HPPD and other disorders is not yet clear, which is why people with HPPD may be improperly diagnosed as schizophrenic or bipolar and treated with depressants that perpetuate their symptoms. Recent imaging of the brain using arterial spin labeling, blood oxygen level-dependent measures and magnetoencephalography have started to examine the changes in the brain on the drug and further research could help physicians more accurately diagnose patients who have taken LSD.

The use of LSD and other psychedelics do not cause schizophrenia or lasting anxiety,
depression or psychosis, but were actually associated with lower rates of mental health problems. Psychedelics could be helpful to treating a number of diseases, including schizophrenia, and the findings that its use in medical environments is safe should push more researchers to discovering immunotherapies with psychedelics. These diseases are not limited to mental illnesses and can be expanded to immune diseases and disorders because of the ability of serotonin receptors to mediate inflammatory responses in the immune system. The short-term benefits should also be considered when discussing medicinal importance of the drug. Most recreational users take LSD in order to expand their cognitive ability, especially through artistic outlets, because of the drug’s ability to make users feel, think and perceive things in ways that they could not have otherwise. This can also be expanded to the medical and public health fields by allowing patients with terminal illnesses to safely take LSD in a controlled environment to not only reduce their anxiety associated with their shortened lifespans, but also to help them expand their cognitive abilities to release any repression of their death consciousness.

References


