A Review of Lysergic Acid Diethylamide (LSD) in the Treatment of Addictions: Historical Perspectives and Future Prospects

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A Review of Lysergic Acid Diethylamide (LSD) in the Treatment of Addictions: Historical Perspectives and Future Prospects

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Abstract: Lysergic acid diethylamide (LSD) is a semisynthetic compound with strong psychoactive properties. Chemically related to serotonin, LSD was initially hypothesized to produce a psychosis-like state. Later, LSD was reported to have benefits in the treatment of addictions. However, widespread indiscriminate use and reports of adverse affects resulted in the classification of LSD as an illicit drug with no accepted medical use. This article reviews LSD's storied history from its discovery, to its use as a research tool, followed by its widespread association with the counterculture movement of the 1960s, and finally to its rebirth as a medicine with potential benefits in the treatment of addictions. LSD's pharmacology, phenomenology, effects at neurotransmitter receptors, and effects on patterns of gene expression are reviewed. Based upon a review of the literature, it is concluded that further research into LSD's potential as a treatment for addictions is warranted.

Keywords: Addiction, entheogen, ergot, hallucinogen, lysergic acid, lysergic acid diethylamide, LSD, psychedelic drugs.

THE DISCOVERY OF LSD

LSD was first synthesized in 1938, while Hoffman was attempting to synthesize a circulatory and respiratory stimulant derived from ergot [1]. Hoffman synthesized the twenty-fifth compound in a series of lysergic acid derivatives, it was named "lysergsäure-diethylamid-25" (German) or "lysergic acid diethylamide-25" (English). More commonly known as "LSD" or "LSD-25", this chemical was found to have strong effects on the uterus. However, it also caused restlessness in experimental animals, which resulted in the suspension of further testing with this compound [1].

In 1943, Hoffman synthesized LSD a second time [1]. After inadvertently absorbing a small amount through his skin, he deliberately self-administered an extremely small dose of this medicine to further explore its effects. After ingesting 250 micrograms, which was the lowest dose he expected would produce an effect, Hoffman experienced a mixture of confusion, dizziness, perceptual distortion, and a fear of going insane. However, he also experienced periods of clear thinking and a perception that his consciousness existed outside of his body [1].

Subsequently, studies were performed on a variety of animals including mice, cats, dogs, chimpanzees, fish, and spiders. In the latter, it was observed that low doses of LSD resulted in the production of webs that were better proportioned than normal webs. However, at higher doses, the webs were poorly constructed [1].

PHARMACOLOGY OF LSD

LSD is a semisynthetic compound consisting of naturally occurring lysergic acid, which is found in all major ergot alkaloids, and a diethylamine group, which is added in the laboratory. Alkaloids are naturally occurring, nitrogen containing organic compounds and include nicotine, morphine, atropine, cocaine, and caffeine. Ergot alkaloids have a variety of medicinal effects including producing uterine contractions, stopping uterine bleeding, and reducing migraine headaches.

LSD's psychoactive effects begin within 20-60 minutes of ingesting the drug and typically last 8-12 hours. The effects are dependent upon dosage, body weight, age, and tolerance [3]. The plasma half-life is 5.1 hours, with a peak plasma concentration at 3 hours post-dose [4]. In humans, the effective dose range is 0.0003-0.001 mg/kg. The minimal psychoactive dose in adult humans is generally considered to be 25 micrograms [2].

Tolerance to LSD's effects develops rapidly, if administration is repeated with too short an interval between doses. For example, if LSD is administered daily, no reaction will occur by the third day [5]. The LD50 varies widely between animal species. In mice the LD50 is 50-60 mg/kg IV whereas in rabbits it is 0.3 mg/kg [1]. A single elephant died after being administered 0.06 mg/kg [6], a dose that was considered to be 99 times too large [7].

Although the lethal dose in humans is not known, it is estimated to be at least 0.2 mg/kg [2]. This means an overdose of 300-600 times the normal effective dose would be required to cause death in humans. To date, there have been no known deaths resulting purely from LSD overdose. However, fatalities have resulted from behaviors that occurred while individuals were under the influence of LSD.

LSD'S EFFECTS ON NEUROTRANSMITTERS AND THEIR RECEPTORS

LSD is believed to exert its pharmacologic properties primarily through its effects on the serotonin system. LSD binds to 5-$HT_{1A/1B/1D}$, 5-$HT_{2A/2C}$, 5-HT_{5A}, 5-$HT_{6,}$ and 5-HT_{7}

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receptors [8]. However, the psychedelic effects of LSD are generally attributed to its partial agonist effects at 5-HT_{2A} receptors. Psychedelics share a common biochemical action in that they all act as agonists at 5-HT_{2A} receptors [5, 9]. Antagonists of 5-HT_{2A} receptors are known to block the psychedelic properties of LSD [8].

5-HT_2 receptors are known to activate phospholipase C (PLC); a membrane bound enzyme that catalyzes the degradation of phosphatidylinositol 4,5-biphosphate (PIP_2) to inositol 1,4,5-triphosphate (IP_3) and diacyglycerol (DAG). IP_3 triggers the release of calcium from intracellular stores. These calcium ions then activate calcium/calmodulin kinases, a group of enzymes that phosphorylate other proteins involved in the regulation of cellular functions. DAG activates protein kinase C (PKC), which stimulates the production of arachidonic acid. The latter facilitates the production of prostaglandins and prostacyclins, which exert numerous effects on cellular processes [10].

5-HT_{2A} receptors also activate the phospholipase A2 (PLA2) signaling pathway and subsequent release of arachidonic acid [5]. Although LSD stimulates the PLA2 pathway to a greater extent that the PLC pathway, the significance of this finding remains unclear [11].

5-HT_{2A} receptors have also been found to couple to phospholipase D (PLD). This enzyme catalyzes the hydrolysis of the terminal diester bond of phosphatidyl choline, producing phosphatidic acid and choline [5].

The relationship between LSD's agonist activity at 5-HT_{2A} receptors and its psychedelic effects on human consciousness has not yet been elucidated. LSD has been found to affect a wide array of neurotransmitter systems in addition to the serotonergic system. LSD binds to adrenergic receptors (α_1 and α_2) [5] and inhibits NMDA transmission in the prefrontal cortex [12]. LSD acts as an agonist at D_1 and D_2 receptors [8, 13-14].

The role of glutamate in LSD's action on the central nervous system has been the focus of increased interest in recent years. LSD enhances glutamatergic transmission in the cerebral cortex *via* stimulation of presynaptic 5-HT_{2A} receptors [11]. Aghajanian and Marek suggested the release of glutamate in the cerebral cortex might be responsible for the alterations in cognition, perception, and emotions following administration of LSD [15].

Metabotropic glutamate receptors, or mGluRs, have been studied as a mediator of LSD's actions. mGluRs are involved in a wide variety of functions including memory, anxiety, learning, and the perception of pain [16]. It has been demonstrated that mGluRs activate biochemical cascades, which effect neuronal excitability [17].

A subset of mGluRs, known as $mGluR_2$s, couple with 5-HT_{2A} receptors to form functional complexes in the brain cortex. These 5-HT_{2A}/$mGluR_2$ complexes have been demonstrated to play an important role in the action of hallucinogenic drugs. For example, activation of $mGlu_2$ receptors inhibits hallucinogen-specific neuronal signaling pathways induced by hallucinogenic 5-HT_{2A} receptor agonists [18]. Furthermore, mice with disrupted $mGluR_2$ signaling capacity are insensitive to the cellular and behavioral effects of hallucinogens [19]. These findings suggest that the 5-HT_{2A}R/$mGluR_2$ complexes may be one of the molecular sites responsible for the actions of hallucinogenic drugs [19].

Svenningsson *et al*. proposed another possible mechanism for LSD's psychoactive effects. They hypothesized LSD's effects are mediated through dopamine- and cAMP-regulated neuronal phosphoprotein (DARPP-32) [20].

LSD'S AFFECTS ON GENE EXPRESSION PATTERNS

LSD alters the expression of genes within cells. Even a single dose of LSD has been demonstrated to alter gene expression patterns [21]. Genes that exhibit differential expression following treatment with LSD include: *c-fos*, *krox-20*, *NOR-1*, *arc*, *IKβ-α*, *sgk*, *Ania3* [21]. Increased expression of these genes, which are involved in a wide variety of cellular functions, alters synaptic plasticity, glutamatergic signaling, cytoskeletal architecture, as well as communication between the synapse and nucleus [21].

PHENOMENOLOGY OF LSD

LSD can produce a profound altered state of consciousness characterized by changes in physiology, perceptions, emotions, and cognition. Some individuals report transcendent or mystical experiences [2]. Specific effects of LSD may include the following:

Somatic Effects

Subjects may experience: changes in heart rate and blood pressure, dilation of the pupils, sweating, hypersalivation, piloerection, nausea, diarrhea, vomiting, fatigue, increased muscular tension, tremors, headache, heaviness of the extremities, and sexual feelings. These effects may result from stimulation of both the sympathetic and parasympathetic nervous systems [27]. Analgesia may occur as well [28].

Perceptual Changes

Perceptual changes occur frequently following the ingestion of LSD [2]. The visual pathway is the sensory modality most commonly affected. Visual changes associated with LSD include: blurring of vision, distortion of three-dimensional space, changes in faces and objects, colors may change or be brighter, and halos or areas of light or color may surround objects. Illusions, hallucinations, and changes in the intensity of light may occur. Visual perseveration or after-images may be present [2].

Auditory changes are less common and include: increased or decreased sensitivity to sound, inability to localize the source of sound, confusion or inability to understand sounds, and auditory hallucinations [2].

Tactile changes are the next most commonly reported sensory modality changes [2]. Kinesthetic changes also occur and include: shaking or vibration phenomena, sensations of pressure, and light-headedness. Changes in body image and out of body experiences are reported [2]. Synesthesias are described as well [2].

Emotional Effects

Emotional responses following the ingestion of LSD vary widely and include: euphoria, depression, anxiety, panic, and irritation [2, 22]. If psychiatric patients are administered LSD, the frequency of negative moods is increased [22]. Suicidal ideation may occur [22].

Cognitive Effects

Cognitive changes include: impaired judgment, shortened concentration span, interposed thoughts, mind wandering, wavelike changes in thoughts, inability to control thoughts, and memory changes. Abnormal thought content includes: ideas of reference, bizarre ideas, and delusions [2]. Increased suggestibility has been reported as well [24]. Positive cognitive changes are also reported. Previously unconscious or preconscious material may emerge into consciousness [25]. New insights into one's self or others are described.

Other Effects

Additional effects of LSD include its consciousness-altering effects. These include: a dream-like character to consciousness and lowering of psychological defenses. Creativity may be enhanced as well [2].

Subjective awareness of the passage of time is frequently altered [2]. Time may appear to speed up, slow down, stop, or run backwards. Some individuals experience themselves as existing outside of time.

Transcendental or mystical experiences have been described. These experiences include: 1) a sense of unity or oneness, 2) insightful knowledge and a certainty that such knowledge is truly real, 3) transcendence of time and space, 4) sense of sacredness, 5) deeply felt positive mood, 6) paradoxicality, 7) ineffability, 8) transiency, and 9) positive changes in attitude and/or behavior [26].

ADVERSE EFFECTS

Cohen was the first to systematically investigate the potential side effects of psychedelic therapy [27]. He conducted a survey of 62 investigators who had studied psilocybin or LSD. Forty-four researchers replied to his questionnaire. The responses included data on psychedelic therapy with nearly 5000 individuals on more than 25,000 occasions. The findings indicated that psychotic breaks, panic attacks, and other psychiatric reactions lasting over 48 hours occurred in 0.8 per 1000 normal volunteers and 1.8 per 1000 patients undergoing therapy [27].

In 1962, Cohen and Ditman described an increasing number of adverse effects associated with LSD-25 administration [28]. They warned that the unsupervised use of LSD increased its potential for serious adverse consequences including antisocial acting-out behaviors, misuse of LSD as part of a pattern of multidrug use, and abuse of the euphoriant property of LSD [28].

The following year, these same authors published a follow up report describing nine cases involving different types of adverse effects including: prolonged psychotic decompensation, depressive reactions, release of preexisting psychopathic antisocial trends, abandonment of social responsibilities, and paranoid reactions [29].

Set and Setting

The effects of LSD are strongly influenced by the set and setting in which the drug is utilized [30]. The term "set" refers to the mindset or mental state of the individual at the time of ingestion. This includes the mood, thoughts, and expectations of the individual. As Von Barr and colleagues pointed out, the phenomena induced by LSD cannot be predicted or understood solely in terms of its pharmacological properties, because the personality of the individuals plays a critical role in determining the drug's effects [31].

"Setting" refers to the physical, social, and cultural environment in which the medicine is ingested. "Social learning," which results from modeling and observational learning, plays an important role by influencing the subjective experience with LSD [30].

USES OF LSD

Following the synthesis of LSD in 1938, human trials were initiated. Stoll administered forty-nine doses of LSD in doses of 20-130 micrograms to twenty-two schizophrenic and healthy subjects. Stoll reported the emotional state of the subjects was "predominantly euphoric" [32].

One of the topics raised in Stoll's paper was the potential use of LSD as a research tool in psychiatry. Similarities were noted to the effects of mescaline, which induced hallucinations. Additionally, low doses of LSD appeared to facilitate psychotherapy by allowing repressed material to flow more easily into consciousness [32].

Sandoz began providing LSD at no charge to physicians and research institutes around the world as an experimental drug for research. It was given the trade name "Delysid" [1]. The prospectus for this medicine suggested it might be useful in analytical psychotherapy as well as in experimental studies on the nature of psychosis [1].

This latter indication formed the basis for LSD's initial use by researchers, who hoped it would provide an opportunity to study mental illnesses such as schizophrenia. This idea, known as the "model psychosis" concept [1-2], suggested LSD might provide new insights into the nature of psychosis by mimicking the psychotic state, an effect known as the "psychotomimetic effect" of LSD [2]. Sandoz proposed that psychiatrists take LSD in order to experience what their patients were experiencing. It was believed this experience would allow them to gain a greater understanding of their patient's mental state. In addition, it was theorized that administering LSD to non-psychotic subjects would cause them to experience a schizophrenia-like state. It was hoped this would provide a model for studying this disease and potentially discovering new and improved treatments for schizophrenia and related psychotic disorders. The model psychosis theory did not begin with LSD, however. Ten years prior to the synthesis of LSD, Beringer suggested mescaline might be used to help psychiatrists better understand the psychotic experiences of their patients [33].

Based upon the observed effects of LSD in experimental sessions, and a rudimentary understanding of the phenomenology induced by this medicine, LSD and related compounds were referred to as "hallucinogens." In 1957, Osmond offered "psychedelic" as a replacement term, contending that these medicines did much more than "mimic psychosis." He preferred the term "psychedelics" because these medicines did not necessarily produce a predictable and pathological sequence of events, but rather could catalyze a "mind manifesting" state involving an enriching and life changing vision [34].

In 1979, Ruck proposed a new term, "entheogen," to describe this class of medicines [35]. *Entheos* is a Greek word which means "god within" and *gen* denotes the action of becoming. Thus, an *entheogen* is a medicine that facilitates the experiencing of opening to the god within.

One outgrowth of the recognition that these medicines did more than produce hallucinations was a decline in the model psychosis concept [24, 36]. Researchers increasingly recognized numerous differences between the psychotic state and the state of consciousness induced by LSD. Bleuler claimed that psychedelic drugs "contributed nothing to the understanding of the pathogenesis of schizophrenia" [37]. Eventually, most scientists renounced the model psychosis theory.

In the 1950's, researchers in Europe and North America began exploring LSD's therapeutic potential [24, 38, 39]. Early reports suggested LSD could enhance the psychotherapeutic process. Not only did LSD appear to expedite psychotherapy, it also showed promise in treating patients who were previously considered poor candidates for psychotherapy. This latter group included alcoholics and narcotic-drug addicts.

LSD AS A TREATMENT FOR ALCOHOLISM

Among the physicians who initially focused on LSD's "psychomimetic properties" were Osmond and Smythies. These researchers proposed a biochemical hypothesis to explain the origin of schizophrenia, suggesting the body might produce an endogenous hallucinogen during times of stress. Their theory was based upon the similarity in chemical structure between adrenaline and mescaline [41]. With time, interest in the model psychosis theory diminished as it was discovered that subjects' experiences with LSD depended greatly on the therapists' and the subjects' objectives [2].

In 1953, Osmond and Hoffer began examining the possibility that LSD might produce a controlled experience similar to delirium tremens. They proposed alcoholics who were administered LSD might have a "hitting bottom experience" that would deter them from ever drinking again [2]. The first two subjects in their study were inpatients suffering from alcoholism. Each was administered 200 micrograms of LSD. One was a male who remained sober for several months after discharge. The other was a female who continued to drink with the same intensity for six months, and then stopped drinking.

Based upon the results of this preliminary investigation, a larger study was designed. The researchers selected the most treatment resistant alcoholics they could find, to compensate for the lack of a control group. They selected alcoholics who had failed every available treatment and whose therapists viewed them as having a very poor prognosis [2].

Twenty-four inpatients were selected. The researchers spent 2-4 weeks establishing a psychotherapeutic relationship with each of the subjects. Subjects were educated regarding the typical effects of LSD. Each subject was then administered a single dose of 200 to 400 micrograms of LSD in a hospital setting. Patients typically spent the day of their LSD treatment in either a private room or a doctor's office. A nurse and/or a psychiatrist stayed with them throughout the day. Initially, there were no efforts made to alter the environment. However, as the study progressed, the researchers began bringing in fresh cut flowers, paintings, and other visual aids to create a more therapeutic environment. The next day, subjects were encouraged to write about their experience.

The results of this study showed that none of the alcoholics were worse after treatment with LSD. Of the 24 alcoholics treated, 12 (50%) were unchanged, 6 (25%) were "improved," and the other 6 (25%) were "much improved." The criteria utilized to define "much improved" included 1) complete abstinence from alcohol for the duration of the follow-up period and 2) lifestyle changed including more stable personal relationships and regular employment [39].

Based upon this early research, Hoffer and Osmond developed a treatment model for patients suffering from addictions. This model, known as "psychedelic therapy," involved one to three sessions in which 300 to 1500 micrograms of LSD was administered each session [2]. The goal was to induce a so-called "psychedelic peak experience" in order to assist the individual in overcoming their addiction. The concept of a psychedelic peak experience was modeled after Maslow's concept of the peak experience [24].

Grof, defined a "psychedelic peak experience" as:

> An ecstatic state, characterized by the loss of boundaries between the subject and the objective world, with ensuing feelings of unity with other people, nature, the entire Universe, and God. In most instances this experience is contentless and is accompanied by visions of brilliant white or golden light, rainbow spectra or elaborate designs resembling peacock feathers. It can, however, be associated with archetypal figurative visions of deities or divine personages from various cultural frameworks [40].

According to Grinspoon, the primary goal of psychedelic therapy was the induction of a mystical experience that would change the way a person sees himself and the world [24]. Grof offered a slightly different explanation, identifying the main goal of psychedelic therapy as the facilitation of "ego death and the subsequent transcendence into the so-called psychedelic peak experience" [40]. Psychedelic peak experiences were viewed as profound experiences that catalyzed recovery from addictions.

In 1959, O'Reilly *et al*. began exploring LSD as a treatment for alcoholism [41, 42]. They administered 200 micrograms of LSD to 68 chronic alcoholic patients who had

not responded to other forms of treatment [43]. Fifteen of the patients received more than one dose of LSD. Patients suffering from any form of psychotic disorder were eliminated from the study. Sixty percent of the patients had been drinking for more than 10 years. Follow-up occurred at varying lengths of time, ranging from two months to 34 months. The results showed that 26 patients (38%) had been abstinent from alcohol during the two months prior to follow-up. The other 42 (62%) were non-abstainers. The only variable reported to correlate with future abstinence was a "transcendental" experience, which the researchers defined as, "a new way of looking at one's life, with a loss of previous defensive meanings or perceptions of oneself" [42]. Unfortunately, the conclusions of this study were limited by methodological problems including: lack of clarity regarding subjects' diagnoses, variable severity of alcoholism, inconsistent follow-up periods, and absence of a control group

In 1962, Jensen published the first controlled trial of LSD as a treatment for alcoholism [44]. This trial was a pilot study involving 145 patients. Subjects were placed in three treatment groups. The first group (65 subjects) received standard inpatient therapy including occupational therapy, two hours of group psychotherapy, three weekly Alcoholics Anonymous meetings, and bimonthly movies with discussion. Near the end of the three weeks of treatment, 200 mg of LSD was administered. The second group (35 subjects) received the same therapy without LSD. The third group (45 subjects) received one-on-one psychotherapy and milieu therapy in an inpatient setting. They did not receive LSD. This was a two-year study with follow-up periods ranging from 6 to 18 months. Of the 65 subjects in the active treatment group (i.e. received LSD), seven (11%) were lost to follow up. Results from the remaining 58 subjects showed 38 (66%) were abstinent throughout the follow-up period, 7 (12%) were improved, and 13 (22%) were unimproved. Among the 35 subjects in the control group (*i.e*. those receiving the same therapy but no LSD), 18 were lost to follow up. Results from the remaining 17 subjects showed 7 (41%) were abstinent, 4 (24%) were improved, and 9 (53%) were unimproved. Of the 45 subjects in the third group (i.e. individual psychotherapy and milieu therapy, but no LSD), 23 were lost to follow up. Among the remaining 22 subjects, 7 (32%) were abstinent, 3 (14%) were improved, and 12 (55%) were unimproved.

Based on the findings of this pilot study, Jensen and Ramsay modified their study design. Their next study involved 125 patients divided into two groups. The treatment group consisted of 70 patients who received milieu therapy, AA group meetings, and LSD treatment. The control group of 55 patients received no LSD. Eight of the treatment group and 26 of the control group were lost to follow-up. Of the remaining subjects, 46 (74%) of the treatment group and 12 (41%) of the control group were improved at six to 18 months post-discharge [45]. This study suffered from multiple methodological flaws including lack of diagnostic specificity, variable periods of follow-up, loss of a large number of subjects to follow-up, and a lack of clarity regarding how improvement was measured.

LSD AND PEAK EXPERIENCES

In 1970, Pahnke *et al*. published a study investigating whether alcoholic patients who reported a psychedelic-peak experience showed greater improvement than patients who did not experience a psychedelic peak experience [30]. This study involved a randomly assigned, double blind protocol with controls. In the active treatment group, 117 subjects received a single 350-450 mg dose of LSD. Control subjects received 50 mg of LSD. A team of independent raters performed evaluations before treatment and 6 months post-treatment. They evaluated "global adjustment" (defined as occupational, interpersonal, and residential functioning as well as the subject's reaction to alcohol) and "drinking behavior." These evaluations found a statistically significant ($p < 0.05$) improvement at six-month follow-up in the treatment group compared with the control group.

Summarizing the existing research into the use of LSD as a treatment for alcoholism in 1967, Hoffer and Osmond reported LSD, when used in combination with other forms of treatment and supportive measures, "results in marked improvement in the recovery rate that would be otherwise obtained" [2]. Grinspoon and Balakar subsequently reported nearly fifty percent of "severe chronic alcoholics" treated with a single dose of LSD remained sober 1-2 years after treatment [24]. The early results from studies utilizing LSD therapy as a treatment for alcoholism were so encouraging, by the late 1960s there were six alcoholism treatment programs in North America utilizing LSD [35].

The encouraging results from these early studies resulted in a growing number of researchers administering LSD to alcoholics. However, not everyone shared in the optimism regarding LSD's effectiveness in the treatment of addictions. Early enthusiasm stemming from promising results was tempered by subsequent criticisms of methodological flaws and inconclusive results.

For example, in an effort to isolate the pharmacological actions of LSD from environmental influences, Smart *et al*. blindfolded subjects and/or restrained them to prevent movement during LSD sessions. Observers were instructed not to interact with subjects who were under the effects of LSD. Although subjects in this study showed some improvement, the results were less positive than in previous studies [47].

REVIEWS OF RESEARCH USING LSD AS A TREATMENT FOR ALCOHOLISM

Several reviews examining the effectiveness of LSD in the treatment of alcohol dependence have been published [24, 48-53]. Mangini published a review in 1998 that found studies of LSD's effectiveness in the treatment of alcoholism were inconclusive [49]. Problems with the reviewed studies included non-random assignment of subjects to treatment groups, failure to use placebo groups or control groups, lack of standardized therapies, absence of blind raters, lack of regard for environmental influences, and inconsistent follow-up.

Abuzzahab and Anderson reviewed 31 studies from 1953 to 1969 involving 1105 alcoholics [53]. They examined five studies involving a single dose of LSD and three studies involving multiple doses of LSD. The authors' conclusion was that meaningful generalizations could not be reached because of inconsistent study designs and criteria for improvement.

Krebs and Johansen performed a meta-analysis of six randomized controlled trials (5 of which were double-blind) examining the efficacy of LSD in the treatment of alcoholism [51]. These trials involved 536 adult subjects who suffered from "alcoholism." Of these subjects, 325 received a single dose of LSD at a dose ranging from 210-800 micrograms. The control group consisted of 211 subjects who received low-dose LSD (25 or 50 micrograms), d-amphetamine (60 milligrams), ephedrine sulphate (60 milligrams), or non-drug control. The conditions during the LSD sessions varied widely as did the preparation and debriefing of subjects. The authors concluded: "The effectiveness of a single dose of LSD compares well with the effectiveness of daily naltrexone, acamprosate, or disulfiram" [51].

More than 20 research articles examining the effects of LSD as a treatment for alcoholism were published from the 1950's through the 1970's. However, research with LSD and other psychedelic medicines slowed dramatically in the 1970's.

LSD AS A TREATMENT OF NARCOTIC ADDICTIONS

Although LSD was studied primarily as a treatment for alcoholism, a few studies examined its potential as a treatment for opiate addiction. Ludwig and Levine explored the use of LSD to treat "narcotic addicts" by administering moderate doses (2ug/kg) to 70 subjects following detoxification [59]. The subjects were randomly assigned to one of five treatment groups: 1) LSD, 2) LSD with psychotherapy, 3) LSD with psychotherapy and hypnosis, 4) psychotherapy without LSD, and 5) psychotherapy with hypnosis. At two-week follow up, subjects demonstrated a significant improvement in self-concept and coping attitudes. However, at two-month follow up, no significant differences were found between the groups. Unfortunately, drug abstinence and behavioral changes were not assessed.

Savage and McCabe examined the use of LSD to treat narcotic addiction [60]. Seventy-four subjects were randomly assigned to a treatment group. Subjects in one group were placed in a halfway house for six weeks where they received psychotherapy followed by a single dose of 200-500 micrograms of LSD. The control group was placed in an outpatient clinic program where they received weekly group psychotherapy. Daily urine samples were used to monitor drug abstinence. After one year, significant differences were found between the treatment group and the control group. In the group who received LSD with psychotherapy, 25% remained abstinent whereas in the control group, only 5% remained abstinent. Of the 13 subjects who had perfect community adjustment scores after one year, 12 reported having had a psychedelic peak experience during their treatment with LSD.

HYPOTHESES REGARDING LSD'S MECHANISM OF ACTION AS A TREATMENT FOR ADDICTIONS

Three hypotheses are suggested to explain LSD's possible mechanism of actions as a treatment for addictions. These hypotheses are not mutually exclusive. Rather, they offer unique perspectives on potential mechanisms by which LSD may aid in the treatment of addictions. These hypotheses, which exhibit some degree of overlap (i.e. individuals may experience anti-addictive effects *via* more than one mechanism of action), include biochemical, psychological, and transcendent mechanisms of action.

Biochemical Hypothesis Regarding LSD's Anti-Addictive Properties

On a biochemical level, addiction has been linked to alterations in the mesolimbic dopamine pathway (MDP) of the brain. Also known as the "reward pathway," the MDP is associated with motivation, pleasure, and reward [56]. The MDP consists of dopaminergic neurons whose cell bodies are located in the ventral tegmental area (VTA) and axonal projections that extend to the limbic system both directly and indirectly *via* the nucleus accumbens (NAc) [57].

Pleasurable stimuli, including drugs of abuse, release dopamine (DA) in the mesolimbic pathway [57-58]. This release of DA in the MDP has been proposed as the common final pathway for the reinforcing effects of all drugs of abuse [57]. Following its release, DA binds to G-protein coupled receptors. It is believed that this release and subsequent binding of DA to receptors is responsible for the "rush" or "high" associated with drugs of abuse and leads to their reinforcing effects [58].

With repeated and chronic administration of drugs of abuse, dopamine levels in the MDP become depleted [59] and DA receptors are reduced in number [60]. This decreased level of dopaminergic tone, which has been termed "allostasis" [61], has been proposed to produce anhedonia and drug craving [61].

One proposed treatment model involves utilizing DA agonists to reduce the craving and withdrawal symptoms associated with discontinuation of DOA's, thereby reducing self-administration [62]. This model is complicated by the fact that DA agonists can themselves become DOA's if they release too much DA. Thus, if DA agonists are to be utilized as effective treatments for addictions, they must release enough DA to return MDP DA to a normal level, but not release too much DA, which would lead to reinforcement and subsequent addiction.

One method of modulating DA levels in the MDP is to administer a 5-HT agonist along with a DA agonist [63]. This concept is based upon the finding that some serotonin neurons exhibit inhibitory effects on DA neurons in the MDP, thus attenuating the reinforcing effects of DA agonists [63].

5-HT agonists exhibit mixed effects on DA release in the MDP, depending upon the particular 5-HT receptor involved. 5-HT_{2C} agonists decrease DA release in the MDP [64]. LSD acts as an agonist at D1 and D2 receptors [8, 13-14], as well as 5-HT_{2C} receptors [8]. *Via* these actions, LSD

is proposed to modulate the release of DA in the MDP, thus alleviating allostasis and restoring homeostasis. This restoration of dopaminergic homeostasis in the MDP would be expected to decrease the reinforcing properties of drugs of abuse.

Psychological Hypothesis Regarding LSD's Anti-Addictive Properties

The psychological hypothesis regarding LSD's anti-addictive properties is based upon the benefits derived from using of LSD in conjunction with psychotherapy. This model of therapy was developed after researchers found that individuals who ingested LSD frequently talked more openly about their problems and exhibited increased insight into the emotional meaning of their symptoms. They also experienced reduced depression, anxiety, and compulsiveness, as well as an increased sense of well-being and increased access to previously unconscious memories [1, 2]. These findings lead researchers to develop a form of treatment involving low doses of LSD integrated with psychotherapy. This was termed "psycholytic therapy." *Psycholytic* comes from the Greek *psyche* meaning "soul" or "personality" and *lysis* meaning "dissolution." Psycholytic therapy was reported to produce dissolution of psychic conflicts or release emotional tension [22]. In doing so, LSD was believed to help resolve the underlying emotional conflicts that perpetuate the addictive cycle.

Transcendent Hypothesis Regarding LSD's Anti-Addictive Properties

A third hypothesis regarding LSD's potential mechanism of action as an anti-addiction medicine stems from its reported ability to produce transcendent, mystical, or peak experiences [22]. Transcendent experiences can produce transformative effects on those who undergo them. A classic example is the transcendent experience of Bill W., the founder of Alcoholics Anonymous. While receiving inpatient treatment for severe alcoholism, Bill W. underwent a profound transcendent experience. As a result of that experience, he stopped drinking alcohol [65].

Recreational Use of LSD

In the 1960's, the use of LSD spread from research laboratories and psychiatric hospitals to the streets of America. This created a "psychedelic movement" in which people began using LSD for recreational or spiritual purposes [66]. Hundreds of thousands of people were drawn to San Francisco in 1967 for the "summer of love" [3].

Unsupervised use by individuals who lacked medical supervision or adequate preparation resulted in widespread abuse and "bad trips." The popular media provided sensationalized stories about how LSD was corrupting America's youth. In April 1966, a Harvard graduate and former medical student was dubbed the "LSD slayer" after he confessed to stabbing and killing his mother-in-law under the influence of LSD. However, it later turned out that he was not under the influence of LSD at the time of the murder. Instead, he suffered from chronic schizophrenia. Nonetheless, *Time* magazine fueled the hysteria by reporting in 1966 that an LSD epidemic was sweeping across America, producing rampant psychosis in America's youth [67].

Adding to the controversy over LSD was its use by two high profile individuals at Harvard University, Timothy Leary and Richard Alpert. Leary and Alpert were strong proponents of the use of LSD in non-medical settings. However, they totally abandoned the scientific method, which they viewed as a "game" they no longer wanted to play. This eventually led to their termination by Harvard [68].

Even within the psychiatric community, the use of LSD provoked controversy. Grinker, the first editor of the Archives of General Psychiatry, wrote an editorial chastising psychiatrists who administered the drug to themselves, claiming they were unqualified as competent investigators [69]. A year later, Grinker wrote in the Journal of the American Medical Association that researchers were using uncontrolled, unscientific methods. He claimed their conclusions were biased by their self-administration of LSD [70].

Numerous social and political issues fueled the growing controversy surrounding LSD. When the Baby Boomer generation came of age in the mid 1960s, they rebelled against their parents' values. A growing dissatisfaction with the status quo resulted in the same corporations that produced an economic boom in the 1950s being blamed for the Vietnam War in the 1960s. A counterculture movement developed that fought for women's rights, civil rights, and free speech. A growing sense of rebellion among America's youth produced anti-war protests and an outgrowth of the Beat Generation known as the "hippies." Fanning the flames of fear about LSD were unsubstantiated claims that this medicine caused brain damage. Such exaggerations were intensified by the thalidomide scare of the late 1950s and early 1960s [66]. The failure of the media and politicians to distinguish monitored, therapeutic use of LSD from unmonitored, recreational use fostered increasingly negative perceptions of this medicine.

Legal Status of LSD

The burgeoning recreational use of hallucinogens and other drugs in the 1960's created escalating social and political pressures to control the use of these drugs. Prior to 1966, there were no state or federal criminal penalties for the unauthorized possession, manufacture, or sale of LSD [24].

However, in 1965 the U.S. Congress passed the Drug Abuse Control Amendments. These amendments, which went into effect in 1966, modified the Food, Drug, and Cosmetics Act and allowed the Secretary of Health, Education, and Welfare to designate hallucinogenic drugs (as well as certain stimulant and depressant drugs) as controlled, thus requiring licensing for their manufacture, sale, or distribution. The Drug Abuse Control Amendments still permitted possession of these drugs for personal consumption or for administration to animals, however [71].

In the spring of 1966, Senator Robert Kennedy, called for congressional hearings. Senator Kennedy, whose wife had been treated with LSD, spoke in favor of additional research rather than greater controls on LSD. Kennedy expressed concern with the FDA's interference with the scientific

investigation of LSD [72]. That same year, Sandoz halted the production and distribution of LSD [24]. This resulted in a marked reduction in the number of research studies investigating LSD's potential therapeutic effects.

In 1968, President Lyndon Johnson issued an executive order creating the Bureau of Narcotics and Dangerous Drugs (BNDD). The BNDD was formed by merging the Bureau of Narcotics, which was responsible for the control of marijuana and narcotics such as heroin, with the Bureau of Drug Abuse Control (BDAC), which had been responsible for handling hallucinogens, depressants, and stimulants. The BNDD was responsible for enforcing the Drug Abuse Control Amendments of 1966. In 1970, the Controlled Substances Act created five schedules for controlled medicines [73]. LSD was placed in Schedule I, the most restrictive of the five schedules. In 1973, the Drug Enforcement Agency (DEA) was established. The DEA assumed responsibility for enforcing the Drug Abuse Control Amendments of 1965, which had previously been the responsibility of the BNDD.

While greater restrictions were being placed on LSD in the United States, controversy over the drug was growing internationally as well. In 1971, the United Nations' Convention on Psychotropic Substances established four Schedules of controlled substances. LSD was placed in Schedule I, the most restrictive of the Schedules [74].

In addition to the increasing legal restrictions placed on LSD, another result of the growing political and social polarization of psychedelics was a perceived schism between "good medicines" and "bad drugs." This lead to the so-called "War on Drugs," a term first coined by President Richard Nixon. The War on Drugs was an effort to stem the tide of illegal drug traffic through military intervention and military aid to foreign countries.

The increasingly restrictive legal climate and social stigmatization of LSD contributed to a precipitous drop in the number of research studies involving LSD in the 1970's. This decline in research was not permanent, however.

RESURGENCE OF RESEARCH

In 1988, the Swiss Federal Office for Public Health gave special permission to resume research with LSD. Research continued in Switzerland until 1993, when all research with psychedelics was again prohibited [75].

In 2007, a group of Swiss psychiatrists was granted permission to study the effects of LSD on anxiety in patients with life-threatening illnesses. This research began in 2008 and ended in 2011. Twelve subjects underwent 30 sessions. Twenty-two sessions involved a therapeutic dose of 200 micrograms of LSD and 8 sessions involved a placebo dose of 20 micrograms of LSD. All 12 subjects reported benefits from the treatment and none reported any serious adverse effects [76].

OTHER USES OF LSD

In addition to its role as a treatment for addictions, LSD also has been studied as a treatment for other psychiatric and medical conditions. For example, Obsessive-Compulsive Disorder (OCD) and depression have been suggested to respond to treatment with LSD [77-79].

LSD was utilized as an adjunct to various forms of psychotherapy including individual psychotherapy, psychoanalysis, and Jungian psychotherapy [2]. This use of LSD stemmed from early researchers' discovery that the effects of LSD were sometimes quite different from those predicted by the "model psychosis theory." For example, rather than being guarded or paranoid, some subjects were able to talk more easily about their problems during their LSD sessions. Increased insight into the emotional meaning of symptoms, improvements in depression, reduced anxiety, reduced compulsions, increased sense of well-being, and increased access to previously repressed memories were additional unexpected findings [1-2]. Busch and Johnson felt LSD might serve as a tool for shortening psychotherapy [80]. A Czechoslovakian study reported LSD produced "good" results as a treatment for personality disorders [81].

LSD has been investigated as a treatment for non-psychiatric disorders as well. In the 1960's, LSD was studied as an analgesic. Administered at doses below psychedelic levels, LSD was found to exhibit potent analgesic properties. Kast and Collins administered 100 micrograms of LSD to 50 patients with severe, intolerable pain. The analgesic effects were stronger than the effects derived from traditional opiates and provided longer lasting reductions in pain [23].

Pahnke *et al*. reported about two-thirds of terminal cancer patients experienced improved mood, reduced anxiety, decreased fear of death, and decreased use of analgesic medication following the administration of LSD [82].

LSD has also been used as a treatment for cluster headaches. Sewell *et al*. studied 53 patients who suffered from cluster headaches. They selected individuals who had used LSD or psilocybin specifically to treat their condition. They found 7 of 8 LSD users reported cluster period termination and 4 of 5 LSD users reported remission period extension following self-administration of LSD [83].

CONCLUSION

Addictions constitute a global health crisis. The 2012 World Drug Report estimated 230 million people use illicit drugs each year and almost 200,000 die from drugs [84]. In 2009, close to 30% of the world population used illicit drugs, alcohol, or nicotine. In areas of Europe, South Asia, and Africa, the rate of prescription drug abuse exceeds the rate of abuse of certain illicit drugs such as cocaine or heroin [85].

The situation is no better in the US. Prescription drug abuse and dependency are growing at alarming rates. Nearly 2 million persons age 12 or older are estimated to have abused or been dependent upon prescription pain relievers in the last year [86]. From 1999 to 2006, the number of fatal poisonings involving opioid analgesics more than tripled in the US from 4,000 to 13,800 deaths [87]. Excessive consumption of alcohol is now the third leading cause of death in the US, with more than 75,000 deaths attributed to excessive drinking in 2001 [88]. The high failure rate of existing pharmacologic interventions for addictions highlights the need for new, more effective treatments.

Early optimism regarding LSD's potential as a treatment for addictions was later replaced by skepticism generated by methodologically flawed studies, widespread misuse, and an increasingly restrictive legal climate. However, a reevaluation of the historical context in which early research took place indicates that such skepticism may have been premature. Some of the contemporary criticisms leveled at early LSD research turn out to be ill conceived. For example, the claim that many studies did not involve a double blind protocol must be reinterpreted from the perspective that the FDA did not require double blind studies until 1962 [89].

If historical prejudices can be overcome, opportunities abound for research into the potential therapeutic benefits of LSD and other consciousness-altering medicines. In countries throughout the world, consciousness-altering medicines have been used therapeutically for thousands of years [90]. Some of these medicines, including ayahuasca [91], ibogaine [92] and mescaline [93], have show promise as potential treatments for addictions.

Furthermore, in this time of increasing globalization, opportunities to learn about the therapeutic potentials of consciousness-altering medicines exist in cultures where these medicines are currently being used in ritual contexts. Collaboration with healers from other cultures who have extensive knowledge and experience with the use of psychedelic medicines could assist in the development of effective treatment strategies for addictions. At the same time, this type of collaboration may help avoid future pitfalls by increasing awareness of the risks associated with these medicines.

A reexamination of LSD's potential as a treatment for addictions indicates that optimism, albeit cautious, may be appropriate. Additionally, an improved understanding of the biochemical basis for addictions supports the possibility that LSD may be an effective pharmacological treatment for addictions. Based upon these findings, it is concluded that further research with LSD as a potential treatment for addictions is warranted.

CONFLICT OF INTEREST

The author confirms that this article content has no conflict of interest.

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