Lysergic acid diethylamide: a drug of 'use'?

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***Abstract*:** Lysergic acid diethylamide (LSD), described as a classical hallucinogen, began its journey from the middle of the last century following an accidental discovery. Since then, it was used as a popular and notorious substance of abuse in various parts of the world. Its beneficial role as an adjunct to psychotherapy was much unknown, until some 'benevolent' experiments were carried out over time to explore some of its potential uses. But, many of its effects were unclear and seemed to be a psychedelic enigma. In this review article, we have described the receptor pharmacology, mechanism of action, effects and adverse effects of LSD on the normal body system. We have also highlighted its addictive potentials and the chances of developing tolerance. We have assimilated some of the interesting therapeutic uses of this drug, such as an antianxiety agent, a creativity enhancer, a suggestibility enhancer, and a performance enhancer. We have also described LSD to be successfully used in drug and alcohol dependence, and as a part of psychedelic peak therapy in terminally ill patients. The relevant chronological history and literature in the light of present knowledge and scenarios have been discussed. Based on available evidence, LSD could be tried therapeutically in certain specific conditions under controlled settings. But as we mention, due to all the safety concerns, the use of this nonaddictive 'entheogen' in actual practice warrants a lot of expertise, caution, cooperation and ethical considerations.

Keywords: abuse, addiction, dependency, hallucinogen, lysergic acid diethylamide, psychedelic

Introduction

In its journey from the middle of the last century, lysergic acid diethylamide (LSD) has been used as a popular and notorious substance of abuse globally. Its putative role in psychotherapy was much less understood, until sporadic experiments were carried out over time to explore some of those properties. In this review article, we have highlighted the receptor pharmacology, mechanism of action, effects, adverse effects and addictive potentials of LSD. We have described some of the interesting uses of this drug in psychiatry, such as an antianxiety agent, a creativity enhancer, a suggestibility enhancer, a performance enhancer, and also its other successful uses like in drug and alcohol dependence, and as a part of psychedelic peak therapy in terminal illness. We have highlighted the relevant chronological history and literature in the light of present knowledge, and suggest that based on available evidence, LSD could be tried therapeutically in certain specific conditions under appropriate settings.

Effects of LSD on the normal system

LSD has been known over the last century as a remarkable hallucinogenic agent. Albert Hofmann, who pioneered the invention of LSD, expressed that psychedelics could see its way into the future through transpersonal psychology. He went on to say, 'It was only through this route of transpersonal psychology that we could gain access to the spiritual world' [Grob, 2002, p. 16]. LSD can be termed an 'entheogen', which means that the user feels 'as if the eyes have been cleansed and the person could see the world as new in all respects' [Ruck *et al.* 1979, p. 145]. It is said to enhance the user's appreciation of the environment, and increases creativity. It also seems to 'open the gates of awareness' to the mind-bending mystical or religious experiences and overall brings profound changes in the user [Passie *et al.* 2008].

LSD is one of the most potent, mood-changing, semi-synthetic psychedelic agents, colloquially measured in 'hits' or 'tabs'. Numerous synthetic

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methods in clandestine laboratories have been used successfully or unsuccessfully to produce this drug. The popular street names are: Acid, Stamp, Lucy, Microdots, Purple Heart, Sunshine, Heavenly Blue, and so on. Its use as a recreational agent started by the early 1960s and popularity continued into the early 1970s.

The effects of LSD are remarkably unpredictable. The effects are due to interruption of the normal interaction between the brain cells and serotonin [Eveloff, 1968]. The usual mental effects are delusions, visual hallucinations, distortion of sense of time and identity, impaired depth and time perception, artificial sense of euphoria or certainty, distorted perception of the size and shape of objects, movements, color, sounds, touch and the user's own body image, severe, terrifying thoughts and feelings, fear of losing control, fear of death, panic attacks, and so on [Liester, 2014].

LSD users often experience loss of appetite, sleeplessness, dry mouth and tremors. Visual changes are among the more common effects; the user can become fixated on the intensity of certain colors. Extreme changes in mood, anywhere from a spaced-out 'bliss' to 'intense terror', are reported [Eveloff, 1968]. Not only do users disassociate from their usual daily activities, but they also keep taking more drugs in order to re-experience the same [Schmid *et al.* 2015].

Behavioral and emotional dangers are often pronounced. Severe anxiety, paranoia, and panic attacks occur at high doses and are called 'bad trips'. Most users express that they had bad trips due to the environment and people surrounding their use [Eveloff, 1968]. Even touch and normal bodily sensations turn into something strange and bizarre. And dangerously, some people never recover from such psychosis. Sensations may seem to 'cross over', giving the user the feeling of 'hearing colors' and 'seeing sounds'. These changes can be frightening and can cause panic attacks. Many LSD users experience flashbacks, or a recurrence of the LSD 'bad trip', often without warning, even long after taking LSD [Eveloff, 1968; LSD Dangers, 2015]. These effects typically begin within 30–60 min after taking the drug and can last for up to 12 h [Schmid *et al.* 2015].

The dosage that is required to produce a moderate effect in most subjects is 1–3 μg/kg body weight. The physical effects produced are: dilated pupils, higher or lower body temperature, sweating or chills, loss of appetite, sleeplessness, dry mouth, tremors, and so on. Stimulation of the sympathetic nervous system can lead to hypothermia, piloerection, tachycardia with palpitation, and elevation of blood pressure and hyperglycemia. These reactions of the autonomic nervous system are not as significant as other effects on the body. Actions on the motor system in the central nervous system lead to increased activity of monosynaptic reflexes, increase in muscle tension, tremors, and muscular incoordination. This latter effect of muscular incoordination is also a symptom of religious ecstasy in many cultures, where the worshipper has such a profound feeling of love of God that he is said to be 'intoxicated by God' [Aghajanian and Marek, 1999].

LSD users may manifest relatively long-lasting psychoses or severe depression, and because LSD accumulates in the body, users develop tolerance. As a result, some repeat users have to take LSD in increasingly higher doses and this increases the physical effects and also the risk of 'bad trips'. Flashback or a sudden recurrence of the user's experience can trigger traumatic or strange experiences, even after many hours or months of abstaining from the drug. Schizophrenia and severe depression may also occur with chronic use [Martin, 1970]. These might result from the modulation of serotonin activity by the action of LSD on central 5-HT_{2A} receptors [Steeds *et al.* 2015; Goldman *et al.* 2007].

Mechanism of action of LSD

The effects of LSD on brain functioning are complex and not fully understood. LSD influences diverse neurotransmitter systems [Nichols, 2004; Passie *et al.* 2008], but its psychosensory effects are mainly mediated by activation of the $5HT_{2A}$ receptors, with significant modulation by $5HT_{2C}$ and $5HT_{1A}$ receptors as well [Nichols, 2004; Vollenweider *et al.* 1998]. No neuroimaging studies have been conducted with LSD, whereas neuroimaging studies with the LSD-related substances psilocybin [Carhart-Harris *et al.* 2012; Gouzoulis-Mayfrank *et al.* 1999; Vollenweider *et al.* 1997] and dimethyltryptamine [de Araujo *et al.* 2012; Riba *et al.* 2006] have yielded inconclusive results, presumably because of the methodological challenges. The few definite results that came out through different studies are activation of the right hemisphere, altered thalamic

functioning, and increased activity in paralimbic structures and frontal cortex.

$5HT_{2A}$ receptor activation is coupled with several intracellular signaling pathways [Halberstadt, 2015]. Gq-mediated signaling activates the inositol triphosphate–diacylglycerol pathway, leading to activation of protein kinase C [Garcia *et al.* 2007]. Signaling through G protein Gi/o, leading to activation of Src and expression of the immediate early genes egr-1 and egr-2, may be necessary to produce the hallucinogenic effects of LSD [Gonzalez-Maeso *et al.* 2007]. The metabotropic glutamate receptor 2 which forms complexes with $5HT_{2A}$ receptors is required for the pharmacological and behavioral effects [Gonzalez-Maeso *et al.* 2008; Moreno *et al.* 2011]. $5HT_{2A}$ agonists activate subpopulations of pyramidal cells in the cerebral cortex by enhancing glutamatergic neurotransmission within the intracortical networks, particularly those involving cortical layer V [Aghajanian and Marek, 1999; Beique *et al.* 2007; Puig *et al.* 2003; Zhang and Marek, 2008]. The human serotonin receptor binding affinities (Ki) of LSD for different serotonergic receptors $5HT_{1A}$, $5HT_{1D}$, $5HT_{2A}$, $5HT_{2B}$, $5HT_{2C}$, and $5HT_6$ are respectively 0.64–4.92 nM, 14 nM, 0.76–21.4 nM, 0.977–8.91 nM, 1.1–45.7 nM, and 2.29 nM.

Tolerance and addictive potentials

The LSD user's reactions are extremely subjective, variable, and unpredictable. Thus one trip may be filled with brilliant hallucinogenic sights and sensations, mind expansion, as well as euphoric feelings of oneness with the universe; while, another trip may bring anxiety, panic, fear, and depression, despair, and solitude of disappointment. An individual's body image may be distorted; the sensations can turn to a 'bad trip' and eventually culminate in frank psychosis. The drug moves quickly to the brain and throughout the body and acts on both the central and autonomic nervous systems. All traces of the drug disappear from the brain rapidly in about 20 min, although the effects may last many more hours.

As mentioned, flashback is a real perturbing side effect. One theory suggests that flashbacks are induced by stress or fatigue, or by resort to other drugs. However, frequent or long-term use of LSD has shown to culminate in tolerance. Emotional, physical, and mental stability return to baseline quickly. As a result, tolerant users require more of the drug to achieve the same effect and invariably invite more trouble.

Abuse of LSD is rather difficult; the drug produces such an absurd high that daily ingestion is almost impossible. Thus LSD use does not lead to physical dependence. However, the tolerance as mentioned disappears after a few days of abstinence without producing craving. So, LSD dependence is typically psychological and not physical [Gable, 1993; Bogenschutz *et al.* 2015].

Is LSD only 'bad'? A brief passage through time

Classic hallucinogens have been used over the past 5000 years [El-Seedi *et al.* 2005], but Arthur Heffter first described the effects of mescaline in late 1800 [Heffter, 1896, 1898]. LSD was first synthesized in 1938, by Albert Hofmann, a chemist working on natural products at the Sandoz AG pharmaceutical company in Basel, Switzerland. As an attempt to synthesize a circulatory and respiratory stimulant derived from ergot, he synthesized LSD. He tried it in experimental animals and found it caused restlessness and had effects on the uterus. It resulted in the suspension of further testing with this compound.

In 1943, Hofmann again synthesized LSD for the second time. This time, he deliberately self-administered an extremely small dose of this compound to explore its effects further. After ingesting 250 μg, which was the lowest dose he expected would produce an effect, Hofmann experienced a mixture of confusion, dizziness, perceptual distortion, and a tremendous fear of going insane [Hofmann, 2009]. Subsequently, studies were performed on a variety of animals. The median lethal dose (LD_{50}) was found to vary widely between animal species. In mice it was found to be 50–60 mg/kg intravenously whereas in rabbits it was 0.3 mg/kg intravenously [Hofmann, 2009].

Following Hofmann's discovery of LSD, there was a surge of scientific work on the classic hallucinogens. During the 1950s, LSD was introduced to the medical community as an experimental tool to induce temporary psychotic-like states in 'normals' ('model psychosis') [Abramson, 1967]. In 1950, LSD was reported as a promising agent [Busch and Johnson, 1950] in permitting extensive recall and abreaction, and in producing an improved

insight. In 1953, Katzenelbogen and Fang published a report using small doses of LSD and mentioned that the drug 'induced a great ventilation of emotion in schizophrenics' [Katzenelbogen and Fang, 1953].

Sandison in 1953 opened the first LSD clinic in England, perhaps to opine that LSD therapy worked best in obsessional neurosis and generalized anxiety [Dutta, 2012; Greer and Tolbert, 1990]. In 1954, Sandison employed varying dosages of LSD in patients with chronic neurosis [Sandison, 1954]. Then in 1955, Frederking mentioned a method in which he used LSD as an adjunct to psychoanalytic therapy [Frederking, 1955]. Almost around the same time, Abramson's group subsequent to 1955 published a number of papers dealing with LSD reactions [Abramson, 1955a, 1955b, 1956, 1967; Cerletti, 1956; Sandoz, 1956; Caldwell, 1958] where they therapeutically employed the drug in a modified psychoanalytic approach.

Psycholytic and psychedelic therapy models of the 1950s through the early 1970s used hallucinogen-assisted treatment to achieve long-lasting personality changes, behavioral changes, and symptom relief, although they emphasized different mechanisms in exerting the therapeutic effects [Grinspoon and Balakar, 1997; Grof, 2008]. However, it was Osmond who coined the term 'psychedelics' and revolutionized their use in chronic alcoholics in 1957 [Osmond, 1957]. LSD has the potential to treat alcoholism according to a retrospective analysis of studies published in the late 1960s [Ungerleider and Andrysiak, 2006].

Toward the end of the 1960s, people began using LSD for recreational and spiritual purposes [Lee and Shlain, 1985]. Clinicians and clinical scientists explored the use of these compounds to facilitate rapid therapeutic effects in addictions, as well as anxiety disorder, major depression, obsessive–compulsive disorder, and other psychotic conditions. LSD and other hallucinogens were legally available for clinical use as an experimental treatment until the mid to late 1960s [Grinspoon and Balakar, 1997]. Research on LSD was conducted by drug companies and the United States of America military. However, controlling the use of the drug became problematic in the 1960s when it began to become popular with the abusive '1960s drug culture'. In 1962, a single dose of 0.06 mg/kg of LSD was administered to a male elephant named Tusko, at the Lincoln Park Zoo in Oklahoma City, and there were rapid changes in the behavior of Tusko and he died after 1 h and 40 min of the said injection [West *et al.* 1962].

LSD (combined with counseling) was found to reduce anxiety, depression, and pain in patients with advanced cancer in the early 1960s [Kast and Collins, 1964]. Other studies with more than 100 patients with advanced cancer established this approach and demonstrated safety and promising results [Kurland, 1985; Yensen and Dryer, 1992]. The psychedelic method was most commonly used then in patients with terminal cancer [Kurland, 1985; Pahnke *et al.* 1969]. Cohen was the first to systematically investigate the potential adverse effects of psychedelic therapy in 1962. Cohen and Ditman described an increasing number of adverse effects with LSD administration and they warned that the unsupervised use of this euphoric drug might increase its potential for antisocial behavior and abuse [Cohen and Ditman, 1962].

In 1973, Savage and McCabe examined LSD for the treatment of opiate addiction [Savage and McCabe, 1973]. In 1979, Ruck and colleagues proposed a new term, 'entheogen' (Greek: to generate the divine within) to describe LSD [Ruck *et al.* 1979]. Workers mostly realized that the effects of LSD were strongly influenced by the mental state of the individual and the physical, social, and cultural environment in which it was ingested [Zinberg, 1984; Barr *et al.* 1972].

The Hallucinogenic Drug Regulations (1967) were introduced to restrict the use of these drugs only by qualified practitioners. It was thus hoped to minimize the risk of harmful behaviors and consequences, which had received extensive publicity in the daily press, and unfortunate experiences resulting from self use and experimentation by the lay public [Barnes, 1970]. Some LSD-assisted psychotherapy however continued in Czechoslovakia, the Netherlands, and Germany during the 1970s [Leuner, 1981] and in Switzerland from 1988 to 1993 [Gasser, 1996]. The National Survey on Drug Use and Health reported LSD to be a major drug of abuse in every annual survey since the 1970s [McGlothlin and Arnold, 1971]. However, today there is an increased interest in research with LSD among clinicians [Sewell *et al.* 2006].

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 [Gasser, 1994–95]. Modern researchers have begun to look at the beneficial uses of LSD again over the last decade, looking for hopeful treatments for Alzheimer's disease, cluster headaches, and various mental illnesses. Evidence clearly suggests that the psychedelics (such as LSD) have a much greater safety profile than other major addictive drugs. LSD use is associated with an extremely low mortality rate and it produces little physical dependence.

Looking at the uses in the present light

Despite LSD's widespread recreational use, no proper and standardized pharmacological or clinical studies have been conducted within the last 40 years. After initial psychiatric investigations by Stoll [Stoll, 1947], several case reports and studies in the 1950s and 1960s described different bizarre psychological effects of this drug in clinical practice [Bercel *et al.* 1956; Rothlin, 1957; Salvatore and Hyde, 1956; Hollister and Hartman, 1962]. However, these studies were not performed according to modern research standards and did not include controlled conditions or systematic characterization of psychotropic effects. Interestingly, after no research on humans for more than 40 years, there is now renewed interest in LSD in psychiatric research.

There is a growing belief that psychedelic drugs possess enormous potential as research tools in psychology and psychiatry [Griffiths and Grob, 2010; Nutt *et al.* 2013; Sessa, 2005], but a clearer characterization and definition of their principal effects on the mind and brain are required to demonstrate why they are important [Carhart-Harris *et al.* 2014]. In addition to the marked hallucinogenic effects, LSD exerts methylenedioxymethamphetamine-like empathogenic mood effects that may be useful in psychotherapy. In a recent study, LSD showed promising results in translational psychiatric research in a controlled clinical setting as it altered sensorimotor gating in a human model of psychosis [Schmid *et al.* 2015; Ungerleider and Andrysiak, 2006].

LSD in drug dependencies

Historically, LSD was reported to be beneficial in the management of drug addiction [Savage and McCabe, 1973]. However, widespread indiscriminate use and reports of adverse effects resulted in the classification of the drug as an 'illicit agent' [Liester, 2014]. In the last decade or so, however, a new generation of researchers was interested in harnessing the therapeutic benefits of some 'illicit drugs' for post-traumatic stress disorder (PTSD), drug and alcohol dependency, and smoking cessation [Frood, 2012].

One study reviewed the use of LSD, peyote, ibogaine, and ayahuasca in the treatment of drug dependencies. Evidence suggests that these substances help in recovery from drug dependency through a variety of therapeutic mechanisms, mostly involving serotonin. These serotonin-based dynamics are directly relevant to treat addiction because in addicted individuals, serotonin levels are usually low, and serotonin also modulates other neurotransmitter systems [Winkelman, 2014; Ray, 2010; Glennon *et al.* 1984; Halberstadt, 2015; Nichols, 2004; Vollenweider and Kometer, 2010]. A meta-analysis of controlled trials has demonstrated a consistent and clinically significant beneficial effect of high-dose LSD in this context [Bogenschutz and Johnson, 2016].

Effects on prepulse inhibition

In an interesting study, LSD (200 μg) and placebo were administered to 16 healthy subjects in a double-blind, randomized, placebo-controlled, crossover study. The outcome measures included psychometric scales, investigator ratings, prepulse inhibition (PPI) of the acoustic startle response, autonomic, endocrine, and adverse effects. LSD produced pronounced alterations in waking consciousness and predominantly induced visual hallucinations, audio-visual synesthesia, and positively experienced derealization and depersonalization phenomena. LSD also increased subjective happiness, closeness to others, wellbeing, openness, and trust. LSD decreased PPI compared with placebo and significantly increased blood pressure, heart rate, body temperature, pupil size, plasma cortisol, prolactin, oxytocin, and epinephrine [Schmid *et al.* 2015]. LSD disrupted PPI and produced sensorimotor deficits similarly to those observed in schizophrenia [Braff *et al.* 1992; Kumari *et al.* 2000; Ludewig *et al.* 2003; Quednow *et al.* 2008] which may be due to its action at $5HT_{2A}$ receptor [Nichols, 2004; Vollenweider *et al.* 1998; Gonzalez-Maeso *et al.* 2008]. It is to be noted that PPI is also influenced by genetic variations in the $5HT_{2A}$ receptor gene [Quednow *et al.* 2009, 2012].

For anxiety associated with life-threatening diseases

Recently completed trials investigating the utility of psychedelics in psychotherapy have demonstrated safety and impressive efficacy in treating anxiety related to terminal diseases [Gasser *et al.* 2014; Grob *et al.* 2011]. In one study evaluating the role of LSD in combating severe anxiety disorder, 100 out of 150 patients with nonpsychotic functional psychiatric disorders benefited from the use of LSD (25–2500 μg). LSD has been considered to permit 'perceptualization of the transference' [Baker, 1964] and extends the scope and value of the psychotherapeutic approach in such cases.

Another double-blind, randomized, active placebo-controlled, crossover pilot study was conducted to examine the safety and efficacy of LSD-assisted psychotherapy (20 and 200 μg) in 12 patients with anxiety associated with life-threatening diseases. At the 2-month follow up, positive trends were found *via* the State–Trait Anxiety Inventory (STAI) scale [Spielberger *et al.* 1970] in reductions in trait anxiety with no acute or chronic adverse effects persisting beyond 1 day after treatment or treatment-related serious adverse events. STAI reductions were sustained for 12 months. These results indicate that when administered safely in a rigorous and supervised setting, LSD can reduce anxiety [Gasser *et al.* 2014].

Recently LSD has been evaluated more in pilot therapeutic trials as treatment for anxiety in patients with life-threatening diseases [Gasser *et al.* 2014; Grob *et al.* 2011; Kupferschmidt, 2014]. Additionally, LSD can increase plasma oxytocin levels and oxytocin is thought to contribute to the empathogenic prosocial effects [Ramos *et al.* 2013]. LSD also increased circulating levels of cortisol and prolactin [Watts *et al.* 1995]. In view of these studies and a recent study using psilocybin [Grob *et al.* 2011], LSD can be explored further for use in such conditions.

To boost human creativity

The idea of using psychedelic (hallucinogenic) agents to boost creative minds in art and literature began in the 1960s [Sessa, 2008b]. The psychological experience induced in humans under the influence of such drugs is purely multifarious and idiosyncratic, but nevertheless a broad range of common characteristics have been identified [Gelade, 1997]. These include alterations in the user's perceptions (in all the sensory modalities), changes in the emotions and expansion in an individual's sense of thought, identity, and creativity [Sessa, 2008b].

Harman and colleagues suggested that using a psychedelic drug under appropriately controlled test conditions satisfies all of the criteria outlined by Rogers [Rogers, 1959] to enhance the creative process [Harman *et al.* 1966]. An attempt to explore the value of LSD in influencing artistic creativity was made in a remarkable long-term series of anecdotal case studies by Dobkin de Rios and Janiger [Dobkin de Rios and Janiger, 2003]. They gave LSD to a mixed group of 60 visual artists over a 7-year period. The artists produced over 250 drawings that were demonstrated to be improved by LSD. Because of the heterogeneity of the population and the aesthetic (nonobjective) nature of analyzing results, making objective statements on how LSD affected the artists' creativity is impossible. However, the drug did appear to enhance certain aspects of the artists' work (more expressionism, sharpening color, greater freedom from prescribed mental sets, increased syntactical organization, deeper accessibility of past impressions and heightened sense of emotional excitement). Even all the artists themselves reported that the LSD experience was artistically and personally profound.

An article by Krippner outlines five studies on the influence of LSD on human creativity [Krippner, 1972]. In a study by Berlin and colleagues, graphic arts were demonstrated to be enhanced by LSD [Berlin *et al.* 1955]. Similar observations were also reported by other scientists [Barron, 1965; McGlothlin *et al.* 1967]. In an experiment by Zegans and colleagues, creativity test data (including the Mednick Association Test, the Modified Word Association Test, the Mosaic Design Test and the Free Association Test) were improved significantly by LSD in 19 graduate students [Zegans *et al.* 1967]. The notable study by Harman and colleagues also demonstrated significantly improved creativity by LSD in a group engaged in creative industries (engineers, theoretical mathematicians, physicists, architects, and designers) [Harman *et al.* 1996].

To enhance suggestibility

The potential of LSD to enhance suggestibility without hypnotic induction was first noted in the 1950s and 1960s [Macy and Abramson, 1960;

Weitzenhoffer and Hilgard, 1959]. This effect was explored in 10 healthy volunteers who were administered intravenous LSD (40–80 μg) in a within-subject, placebo-controlled design. Suggestibility and cued mental imagery were assessed using the Creative Imagination Scale (CIS) [Wilson and Barber, 1978] and a mental imagery test (MIT) scale [Sheehan, 1967]. In comparison to placebo, with LSD, the volunteers gave significantly higher ratings for CIS but not MIT. The magnitude of suggestibility enhancement was however positively correlated with trait conscientiousness which is again related to ego control. These results implied that improved suggestibility may have implications for the use of LSD as an adjunct to psychotherapy [Carhart-Harris *et al.* 2015]. In another study involving 24 healthy participants, suggestibility was significantly enhanced by LSD and mescaline [Sjoberg and Hollister, 1965]. LSD has also been shown to improve suggestibility most in patients with neurosis and schizophrenia, but least in patients with depression [Middlefell, 1967]. $5HT_{2A}$ signaling has been linked to increased cognitive flexibility [Boulougouris *et al.* 2008; King *et al.* 1974], associative learning [Harvey, 2003; Romano *et al.* 2010], and increased neural plasticity in the cortex [Gewirtz *et al.* 2002; Vaidya *et al.* 1997], which may be a prerequisite for improvement in suggestibility. It is also important to note that there are negative and positive implications of enhanced suggestibility with psychedelics like increased danger of inducing false memories or instantiating particular wrong beliefs [Rosen *et al.* 2004].

For treatment of alcohol addiction

LSD is considered as a valuable tool in hastening successful results of psychotherapy in alcoholics who are otherwise difficult to treat [Barnes, 1970; Roberts and Hruby, 1967]. In the 1950s through to the early 1970s, over 30 publications reported on these effects [Abuzzahab and Anderson, 1971; Halpern, 1996; Mangini, 1998; Dyck, 2006; Grinspoon and Bakalar, 1997]. Early reports of clinical outcomes and uncontrolled trials had variable but encouraging results, particularly when the psychedelic model was used [Abuzzahab and Anderson, 1971]. At least a dozen trials with some form of control group were ultimately used [Krebs and Johansen, 2012; Miller and Wilbourne, 2002], but these studies were mostly underpowered and the results were not confirmatory [Johnson, 2008].

The study by Krebs and Johansen was the first ever quantitative meta-analysis of LSD alcoholism clinical trials. Of 536 participants in six trials, 59% of subjects receiving LSD (210–800 μg) reported lower levels of alcohol misuse compared with 38% of subjects receiving placebo [Krebs and Johansen, 2012; Bowen *et al.* 1970; Hollister *et al.* 1969; Ludwig *et al.* 1969; Pahnke *et al.* 1970; Smart *et al.* 1966; Tomsovic and Edwards, 1970].

Psychedelic trip in the terminally ill

End-of-life issues, including pain management and palliative care, are increasingly recognized as significant public health concerns. Anxiety, depression, chronic pain, as well as unresolved family and relationship issues can become potentially serious problems [Howell *et al.* 2010]. High doses of LSD (300 μg or more) sometimes in combination with other hallucinogens as psychedelic therapy were used [Sherwood *et al.* 1962; Savage *et al.* 1964]. In 1964, Kast and Collins published their work on LSD, comparing its pain-relieving effects with opiate analgesics on a group of patients having severe physical pain including patients with cancer [Kast and Collins, 1964]. An administered dose of 100 μg of LSD remarkably reduced the intensity and duration of the pain. Sleep seemed to improve and patients were less occupied with death [Grof and Halifax, 1978]. What was initiated as psychedelic therapy was soon dubbed as 'psychedelic peak therapy' in terminally ill patients as patients used to attain a 'peak transcendental experience' with high doses of psychedelics (350–400 μg) [Pahnke *et al.* 1970]. In these patients, LSD gradually turned out to be a better drug [Dutta, 2012]. This use was extended in the same group of patients to explore the effects on psychological aspects of attitudes, emotions, and sleep patterns associated with terminal illness and death.

As the classical psychedelics (LSD and psilocybin) are nonaddictive [Hofmann *et al.* 1958a,b; Sessa, 2008a; Hasler *et al.* 2004; Fantegrossi *et al.* 2004], current researchers are bringing back these drugs for their exceptional use in relieving the existential agony that comes with terminal illness [Dutta, 2012]. Most of the current research is being targeted at patients who have developed secondary anxiety-related disorders associated with end-stage disease (cancer), and refractory to conventional anxiolytic therapy [Sessa, 2008a]. In fact, recently a small pilot study of psilocybin-assisted psychotherapy with patients with

advanced-stage cancer in the United States obtained promising results [Grob *et al.* 2011] and several additional studies are currently ongoing.

Possible mechanism of action of LSD in addiction

The main mechanism of action of LSD in addiction may be related to binding at serotonergic and other receptors in the brain [González-Maeso *et al.* 2003; Halberstadt and Geyer, 2011]. Increased $5HT_{2A}$ receptor binding has been reported in people with depression [Shelton *et al.* 2009], neuroticism [Frokjaer *et al.* 2008], borderline personality disorder [Soloff *et al.* 2007], impulsive aggression [Rosell *et al.* 2010], and completed suicide [Anisman *et al.* 2008]. Furthermore, frontolimbic $5HT_{2A}$ receptor density is positively correlated with increased anxiety and an exaggerated stress response [Frokjaer *et al.* 2008]. It is well established that anxiety and stress are important triggers for relapse to substance abuse [Sinha and Li, 2007], and so it is possible that $5HT_{2A}$ receptor downregulation by hallucinogens could help in stress-induced relapse in substance abuse [Buckman, 1967].

Another possibility for the mechanism of action of LSD is that classic hallucinogens have effects on expression of brain-derived neurotrophic factor (BDNF) and glial cell line derived neurotrophic factor (GDNF). BDNF and GDNF play critical roles in neurogenesis, synaptic plasticity, learning, memory, and so on [Ghitza *et al.* 2010]. There is some evidence that classic hallucinogens can induce neuroplastic changes, suggesting a basis for persisting behavioral change. Through it acts mainly on $5HT_{2A}$ receptors, LSD and similar drugs also induce remodeling of pyramidal cell dendrites [Jones *et al.* 2009]. The effects of classic hallucinogens on adult neurogenesis have not been established, although a recent study tried to explore these effects [Catlow *et al.* 2013].

Clinical work with classic hallucinogens has emphasized the central role of the patient's conscious experience during the drug's acute effects [Grof, 2008; Hoffer, 1967; Masters and Houston, 2000; Pahnke *et al.* 1970; Sherwood *et al.* 1962]. A 'mystical type experience' by these drugs can lead to long-lasting behavioral changes, increase in the personality dimension of openness, and 'spiritual awakening' in alcoholics [Forcehimes, 2004; Maclean *et al.* 2011]. A number of interesting hypotheses have been proposed as possible mediators of these effects [Bogenschutz and Pommy, 2012]. The published pilot studies of psilocybin for alcohol or nicotine dependence have reported decrease in craving and increase in self-efficacy [Bogenschutz *et al.* 2015; Johnson *et al.* 2014]. Positive behavioral changes and improvements in the feeling of wellbeing and satisfaction with life have also been shown [Griffiths *et al.* 2011]. One process that bears some resemblance to this mystical type experience is the pathogenesis of PTSD where an overwhelming psychological trauma can cause persisting harmful changes in brain structure and function, and sometimes lead to permanent psychological change [Leuner, 1967]. It has therefore been proposed that mystical experiences occasioned by classic hallucinogens can have some inverse-PTSD-like effects [Garcia-Romeu *et al.* 2014].

Safety issues

The potential for classic hallucinogens in addiction treatment requires an understanding of the risks and safety mechanisms to minimize all potential harm. A broad exploration of risks and proposed safety issues has been previously described. Although classic hallucinogens can be used in dangerous ways in nonclinical settings, they do not normally engender compulsive drug-seeking behavior (addiction) as with most other abused drugs (like opioids, cocaine, methamphetamine, and cannabis) [Fantegrossi *et al.* 2008]. It appears that nonmedical use of classic hallucinogens can precipitate prolonged psychiatric reactions (e.g. psychosis) in rare cases [Cohen, 1960; McGlothlin and Arnold, 1971]. Also, classic hallucinogens have very low physiological toxicities, with no evidence of resulting organ damage or neuropsychological deficits even at very high doses [Gable, 1993; Strassman, 1984]. On rare occasions, nonmedical use of such drugs may result in clinically distressing persisting perceptual abnormalities (e.g. hallucinogen persisting perception disorder or flashback). However, such cases have not been observed in clinical research, and are perhaps related to factors absent in research settings (e.g. poor control of dose, poly drug use, etc.). For the large majority of participants, the most relevant safety concern is the potential for dangerous and erratic behavior resulting from the intense subjective experiences with these drugs.

However, the absolute contraindications of LSD use are physical conditions precluding marked excitement (e.g. cardiovascular disease), pregnancy, epilepsy, paranoid personality, overt psychosis, organic-toxic cerebral disorder, and so on. In some species of laboratory animals, teratogenic effects of LSD have been demonstrated by some workers which were, however, not confirmed by others [Barnes, 1970].

Before we move on with LSD

The great value of LSD lies with its 'mystical experience' and 'self realization'. In a properly structured therapeutic setting, the patient can quickly develop a level of 'self understanding' and 'self acceptance'. With the therapist's help, he or she can clearly see the inadequacies in the value system which has underlain previous behavior. With the gain in 'openness' and altered understanding, the patient tries to improve and alter the previous wrongs [Blewett and Chwelos, 1959].

So, when it comes to the caregiver, the therapist must have a thorough knowledge of the patient's psychopathology. He should not attempt hallucinogenic drug therapy until he and the patient have known each other long enough to acquire mutual familiarity and respect.

The indications of LSD-assisted psychotherapy may be courageously listed as psychoneurotic disorders, conversion phobic depressive disorders, neurotic depressive reaction, reactive depression, other (mixed psychoneurosis, pan-neurosis, pseudo neurotic schizophrenia, borderline or latent schizophrenia) personality disorders, cyclothymic (obsessional) and passive-aggressive (obsessional) compulsive sexual deviation addiction, transient situational personality disorders, and manic-depressive reaction in remission [Baker, 1964].

If such therapy is decided upon, it must be by mutual consent. The patient should be acquainted with the difficulties and dangers inherent in this form of therapy, including the question of teratogenicity. No treatment should ever be undertaken other than in a controlled, supervised, structured hospital setting. The therapist must be committed throughout the session and must never leave the treatment precincts until he or she is fully satisfied about the patient's condition. The therapist must be also prepared to abide by the ethical and regulatory principles in a careful and conscientious manner. Finally, it is to be borne in mind that any nontherapeutic uses of these drugs, either by clinicians or patients, are unethical, immoral and illegal, and breach of this code must not occur [Barnes, 1970].

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The authors declare that there is no conflict of interest.

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