LYSERGIC ACID DIETHYLAMIDE

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ABSTRACT

Lysergic acid diethylamide (LSD) is a drug known for its hallucinogenic properties especially at high doses and in recent years has been used as a pharmacological model to study the neurological substrate of psychosis, the effect of antipsychotics, and, in recent decades, the possibility of using it as a remedy for some diseases is being studied.

The purpose of this review is to analyze reference reports published in Pubmed, Web of Science, Scopus, Google Scholar, articles on preclinical and clinical studies related to LSD, history of use, pharmacokinetic properties, mechanism of action by activating serotonergic, dopaminergic, glutamate receptor systems, $TAAR_1$ receptors, amine receptors and effects on the rewarding brain system, pilot preclinical and clinical studies as a therapeutic model for the treatment of depression, anxiety, stress and addictions. We have considered acute psychotic dose-dependent intoxications and chronic psychosis.

Keywords: *LSD, LSD psychosis, LSAD schizophrenia 5-HT2A, LSD acute intoxications, LSD chronic intoxications*

CLASSIFICATION

Lysergic acid diethylamide (LSD) ($C_{20}H_{25}N_3O$) belongs to the class lysergamides or ergoalkaloids. In nature, they are found in the fungus *Claviceps purpurea* growing on cereals, mainly rye. LSD is classified as a drug, psychoactive substance, hallucinogen and entheogen/substance for shamanic, mystical and religious purposes. As a drug it is on List I (USA); Class A (UK); List III (Canada); Annex 1 (Bulgaria). In Bulgaria, possession, production and trade in LSD are prohibited and prosecuted.

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HISTORY

The hallucinogenic properties of the fungus *Claviceps purpurea* have been known for millennia.

The fungus *Claviceps purpurea* (Fries) grows as a parasite on the pistil of some cereals, mainly on rye. It is currently collected as a poisonous herb from which various alkaloids, nitrogen-containing compounds and ballast substances are isolated. The most important are the ergoalkaloids: ergotamine, ergosine, ergozinine, ergocristine, ergocristinine, ergocryptine, ergocryptinine, ergocornine, ergocorninine, ergometrine (ergobazin), ergometrinin (ergometrine). An integral part of these alkaloids is lysergic and isolysergic acid. In folk medicine it is used to induce abortion and as gynecological remedy. In homeopathy, medicines based on it are used to treat blood circulation, with paresthesia and gangrene. In medicine they are used as drugs for neuroses and migraines /belergamine and cofergamine/, to stop uterine bleeding, and to strengthen the contraction of the uterus /ergot/.

Claviceps purpurea and its hallucinogenic properties have been known for centuries. It is believed that it was used in ancient Greece in the so-called Eleusinian Mysteries /annual celebrations dedicated to Demeter and Persephone/. The participants drank a drink of barley or rye, fell into a mystical trance with bright pictures sent to them by the gods. In the Middle Ages, *Claviceps purpurea* became the cause of mass poisoning by falling into the flour. Poisoning with it is called ergotism. Symptoms include muscle twitching and convulsions, inability to control the body, grimacing, confusion, hallucinations, vomiting and diarrhea. They attributed these symptoms to the possession of an evil force. In France, the most common epidemic outbreaks of ergotism have been described, killing thousands of people (about *50* 000 people between 990 and 1130). They called it ergotism and Holy Fire or St. Anthony's Fire, because the patients were hospitalized in St. Anthony's Hospital. The Salem Witch believed to have been caused by ergotism (1,2,3).

The connection between the consumption of flour infected with the fungus was first made by the German physician W. Thelius in 1596, and later by the French physician Dr. Thuillier in 1670. They believed that the disease was not infectious, but was due to rye containing ergotoxins. The first microbiologist to observe the fungus now known as *C. purpurea* was Louis Rene Tulasne in 1853, who suggested that it produced ergo-alkaloids, not rye itself.

Synthesis of LSD Lysergic Acid Diethylamide

The chemical isolation of ergo-alkaloids took place in 1918 and the vasoconstrictor properties of ergotamine were proved. In 1938, the Swiss chemist Albert Hoffmann (later called the „father of LSD") synthesized lysergic acid diethylamine, or LSD-25, from ergot alkaloids in the Sandoz laboratories in Switzerland. Hoffmann himself tried the newly synthesized substance and described his first experience with LSD as „a journey into the universe of the soul, waves of immeasurable happiness flowing through the body." In his memoirs he writes: „I have experienced the grace of God" and the feeling that „God is in everything" (4). It was initially thought to be an effective drug for treating schizophrenia and was used in the mentally ill (5).

The Hippie Period of LSD

The mid-20th century, 1960-1980s, were known as the "hippie period". They are largely due to the research of psychiatrists F. Leary /USA/ (6) and Stanislav Grof /Czech Republic/ (7). These scientists saw in LSD a „magic elixir" expanding consciousness. Adherents of this theory became students, musicians, actors, writers, artists, as well as many hipsters and hippies. LSD is associated with groups that disagree with the prevailing cultural and political situation in the United States and other countries, the psychedelic revolution (8), and the hippie movement (9). Young people who committed crimes ended up in psychiatric clinics and committed suicide. The National Survey on Drug Use and Health (NSDUH) estimates that more than 22 million (9.1% of the US population) have used LSD at least once in their lives (8). LSD was recognized as a drug criminalized in 1965 and banned in the early 1970s, both in the United States and in most countries.

However, lysergic acid diethylamide continued to be studied by psychiatrists, therapists, military and intelligence agencies in the following decades with varying success (10), and in the last decade there was a renaissance in the study of this substance to understand brain neurotransmitters and function, as well as therapeutic means.

Modern Renaissance of Psychedelics as Medicines

Scientific interest in serotonergic psychedelics has increased dramatically over the last decade due to the ineffectiveness of available drugs and the search for alternative approaches, such as translational psychedelic biomedicine for patients. Preclinical and clinical pilot studies with LSD, psilocybin and mescaline, in combination with psychotherapy in volunteers (11, 12, 13), reported good results in the treatment of mood disorders (14), anxiety (11,15,16), depression (12,16,17), post-traumatic stress disorder, cancer and fear of impending death (12,17), increased emotional empathy in healthy volunteers (18), functional neurological disorders (19), inflammatory diseases (11), as well as addiction to tobacco, alcohol (11,12,14,16,17,20,21) and other drug addictions such as cannabis, stimulants and opiates (13).

The potential antidepressant, anxiolytic and anti-addictive effects (17,20,22,24) have been stud-

ied. The putative mechanisms include acute destabilization of the brain network (serotonin, dopamine and glutamate neurons) resulting in its recovery (11,23,25), as well as changes in the expression of genes that contribute to synaptic plasticity, providing physiological evidence that these compounds cause permanent changes in the brain (15,25-27).

Many of these studies are at an advanced stage, but no study to date has shown sufficient efficacy (17,19). For example, a study of 536 volunteers with chronic alcoholism treated with controlled LSD intake showed OR, 1.96; 95% CI, 1.36-2.84; p = 0.0003 (28). Another study of 343 respondents addicted to alcohol, assessed as severely addicted, and using medium and high doses of LSD or psilocybin at home, showed that 83% of them, after that, no longer met the criteria for severe alcohol dependence and reduced drinking (29). A recent online study in the United States of 444 cannabis, stimulant and opiate addicts found that drug addiction was estimated to be 79% severe before psychedelic use, and after LSD and psilocybe use at home, the severity score dropped to 28% (13). All participants shared that they approved of „psychedelic-related changes in life priorities or values such as facilitating reduced alcohol and other drug abuse." Although these results do not seem convincing, the authors conclude that "naturalistic psychedelic use can lead to the cessation or reduction of problem alcohol and drug use" (13,29). Another online study with similar findings surveyed 358 tobacco addicts (21). The results showed that after using psychedelics at home, 38% quit long-term smoking within the next 2 years, and 28% reduced the amount of cigarettes, affective withdrawal symptoms such as depression and cravings were more tolerable. The authors conclude that psychedelics are a promising treatment for tobacco dependence through spiritual experiences, changed priorities and values, and improved emotional regulation (21).

EXPOSURE WAYS

Mucosal resorption, ingestion, snorting and intravenous administration are known. Doses are measured in micrograms (μg) and the dose can vary between 100 and 500 μg.

The most common way of exposure is oral administration, with micrograms of LSD placed on blotting paper. The blotting paper (usually decorated and perforated) is divided into about 1/4 squares, called sections, and soaked in a dilution of lysergic acid diethylamide. A separate section usually contains between 30-100 μg LSD, and the variations are wide depending on the skills of the chemist.

It is also possible to take it in the form of gelatin. They are known as „window glass". Gelatin LSD is made by mixing liquid LSD with gelatin and forming it into small, thin squares. The benefit of this method is that less of the LSD is exposed to the sun and air, which breaks down lysergic acid diethylamide. One square of gelatin usually contains 50-150 μg of LSD.

Liquid LSD is soluble in water and other solvents, although liquid LSD is usually soluble in ethyl alcohol or water. Liquid LSD is used for placement on blotting paper to form labels, but can also be used for intravenous administration. One drop of a powerful LSD liquid can be 50 times the normal dose, although it is usually diluted to the point where one drop equals approximately one dose. This varies considerably from batch to batch and is sometimes a weak dose, while other times it is a very strong dose. It is often stored in small dropper bottles. The use of liquid LSD carries the greatest risk of overdose. The liquid form can be administered by nasal insufflation or by intravenous injection.

TOXICOKINETICS (ADME)

Absorption (A): LSD is rapidly absorbed through the mucous membranes. The initial clinical effects begin after 15-20 minutes.

The maximum plasma concentration is reached within 60 minutes after ingestion, and the plasma concentration depends on the dose taken, for example, at 200 μg it is twice the plasma concentration at 100 μg (30). In an experiment with healthy volunteers (31) who received 200 μg of LSD, the lowest measurable plasma concentration was> 0.1 ng/mL within 12 hours of dosing. The maximum measurable plasma concentration is 4.5±1.4 ng/mL, reaching 1.5 (0.5-4) hours after administration. The concentrations then decrease with a half-life of 3.6±0.9 hours (31).

Distribution (D): Plasma protein binding is greater than 80% and the volume of distribution is 0.3 l kg -1.30.

The most significant amount of LSD penetrates the central nervous system, concentrating in the visual brain areas and the reticular activating sys-

tem (30,32-35). The effects measured in a controlled study started between 21 and 48 minutes after taking LSD at doses of 200 μg and 100 μg in the mouth (30).

Metabolism (M): LSD is metabolized to metabolites (nor-LSD and OH-LSD) by deacylation reactions (36). The metabolite 2-oxo-3-hydroxy LSD / (OH-LSD) is the major human metabolite, the detection and quantification of which is important for clinical and forensic toxicology (37-39).

In vitro controlled studies have shown that liver microsomes are slightly involved in the formation of metabolites (<1% metabolites) for 4 hours. Other isoforms of CYP 450 show a significant contribution, for example, CYP2D6, 2E1 and 3A4 to the formation of nor-LSD, and CYP1A2, 2C9, 2E1 and 3A4 significantly participate in the formation of OH-LSD (38). OH-LSD shows significantly lower affinity and activity to serotonergic receptors compared to LSD and has no hallucinogenic properties, while nor-LSD has hallucinogenic properties similar to LSD. These data suggest that genetic polymorphisms and drug interactions could affect the pharmacokinetics and pharmacodynamics of LSD (38).

The elimination half-life $T_{1/2}$ is 2 to 5 hours, and at a dose of 200 μg it is 8.9 ± 5.9 hours. Minimal amounts in the blood can be detected up to 12 hours after ingestion (30,31).

A study in 13 patients showed that, when taken orally at 160 μg LSD, LSD was detected in the blood from 2 to 5 hours (40).

Excretion: Less than 1% is excreted as unchanged LSD compound and 13% as the OH-LSD metabolite. Elimination is linear and ends in the order of 12 hours at 100 μg and 24 hours at 200 μg (30,31).

Intravenous Administration

When administered intravenously at a dose of 2 μg/kg, the mean plasma half-life is 175 minutes (30).

TOXICODYNAMICS / MECHANISM OF TOXIC ACTION

Threshold Dose

The subjective effects after taking LSD are dose-dependent (18,30,31).

The threshold dose is 10-20 μg, a low dose is 20-75 μg, a dose causing the usual effects is 50-150 μg, a strong dose is 150-400 μg, and a very strong dose is over 400 μg.

The lethal dose is 12 000 μg, which is 30 times the „strong" single dose (18).

The effects at a dose of 100 μg LSD start after about 20 to 40 minutes, the average duration of the effects is about 8 hours (between 5 and 14 hours). Peak effects are observed on average on the third hour of intake (between 1.2- 4.6 hours) (30).

The effects at a dose of 200 μg also start after about 20 minutes, the average duration of effects is about 11 hours (between 6 and 19 hours). Peak effects are observed on average in the second hour of intake (between 0.8-4.4 hours) (30).

Specific mystical experiences, according to a controlled study, show that transcendental experiences do not correlate with plasma LSD concentrations (42).

Individual Sensitivity

Different people have a pronounced individual reaction to a single dose of LSD. Some respond poorly, while others have pronounced toxic effects of the same dose. The explanation for this is the phenotypic difference in the sensitivity of serotonin and dopamine receptors (43).

Mechanism of Toxic Action

Numerous studies on LSD psychosis have shown that lysergic acid diethylamine affects many brain structures, the so-called pleiotropic action. LSD affects brain neurotransmission (via serotonin, dopamine, trace amino acids $TAAR_1$ and glutamate receptors); changes brain activity; acts on the frontal lobe of a rewarding brain system and activates the sympathetic autonomic nervous system.

Serotonin System and LSD

LSD is structurally similar to serotonin. This leads to the idea that serotonin is involved in the pathogenesis of psychosis, which is now considered a well-known fact. LSD acts as a complete or partial agonist of the serotonin receptors 5-HT_{2A}, 5-$HT_{1A,}$ and 5-HT_{2C}. The hallucinogenic potency of LSD is due to binding to the 5HT2A receptor (44-47), while binding to 5-HT_{1A} and 5-HT_{2C} receptors has modulating functions (48-51).

Dopamine System and LSD

Numerous studies in recent years have shown that the pathogenesis of psychosis is due not only to activated serotonin receptors, but rather to the connection between serotonin and dopamine neurons (52,53).

LSD stimulates dopamine D_1 and D_2 receptors (54-58). LSD binds to the D_1 and D_2 receptors as a partial agonist (59) and to the D_4 receptor as a full agonist (60).

The studies of Bunzow et al. in 2001 (61) on rats and subsequent studies (62,63) demonstrated that $TAAR_1$ receptors, widespread in the brain and peripheral nervous system, were involved in the pathogenesis of psychosis by interaction with the dopaminergic system. These receptors are G-coupled and are stimulated endogenously by so-called trace amines (TAs), a subset of biogenic amines, including phenylethylamine (PEA), p-tyramine (pTyr) and tryptamine, formerly referred to as false neurotransmitters (61,64-68). Abnormal levels of TAs have been linked to a variety of neuropathological disorders, including schizophrenia (69-74), major depression (74), Parkinson's disease (75-78), and bipolar disorder (78, 79).

Studies show that these receptors are exogenously stimulated by amphetamines, methamphetamines, ecstasy, and LSD. Stimulation of $TAAR_1$ receptors leads to the production of cAMP and abrupt activation of dopaminergic neurons D_2 in the ventral tegmental region. D_2 receptors in the mesolimbic dopamine system mediate not only psychotic symptoms but also the brain's reward system, particularly the nucleus accumbens, which is considered the brain's „pleasure center" (71,80,81). In recent years, $TAAR_1$ receptors have been identified as a new therapeutic target in the treatment of psychotic disorders, an important modulator of the dopaminergic, serotonergic systems (64-68), and, potentially, the glutamatergic system (64).

LSD and Glutamatergic Receptors

In 1999 and later in 2006, it was demonstrated that LSD, despite its partial action through $5\text{-}HT_{2A}$ receptors, induced phase over-release of glutamate on neurons in the prefrontal cortex (82-84).

LSD and the prefrontal cortex (PFC) are an integral part of the brain's reward system.

The effect of LSD on PFC is through the action (activation) of serotonergic, dopaminergic, $TAAR_1$ and glutamatergic neurons, the terminal ends of which end in the prefrontal lobe of the brain (85). Most of the psychotic and cognitive effects of LSD are on PFC (86).

PFC contains pyramidal glutamatergic neurons, which are modulated by several neurotransmitter systems - gamma aminobutyric acid (GABA) interneurons, dopaminergic, noradrenergic, serotonergic, glutamatergic and cholinergic neurotransmitters. It is now known that any change in these systems as part of the PFC can lead to a change in behavior (87).

LSD interacts with adrenergic receptors and stimulates the sympathetic autonomic nervous system.

LSD stimulates adrenergic receptors (88). Activation of the sympathetic system leads to increased systolic and diastolic blood pressure, tachycardia, hyperthermia, sweating, convulsions, increased muscle tension, tremor and muscle incoordination (18,30,88-91).

EXPERIMENTAL STUDIES

In vitro

In vitro data on leukocyte treatment with LSD indicate that chromosomal fractures and mitotic suppression occur in leukocyte culture. Other studies show that LSD has mild mutagenic effects (92). In vitro cell cultures of human cloned D_2 receptors were assayed for LSD activity (93,94).

Animals

Numerous animal experiments have been performed with LSD to elucidate the pathophysiology of psychosis and schizophrenia caused by LSD (95); the chronic effects on the behavior of animals at long exposures (96); acute psychosis due to serotonin mediation (53,80,97-99), dopamine (55-58,61,99,100), glutamate (83,84); activation of $TAAR_1$ receptors (80), as well as the efficacy of antipsychotic drugs (55). With acute and short-term exposure to large doses of LSD, rats develop acute respiratory failure and rabbits - hyperthermia.

It is claimed that LSD does not lead to physical dependence in humans, so controlled studies on the long-term effects of LSD have only been studied

in animals (33,96-105). Chronic administration of LSD at doses of 0.08 and 0.16 μg/kg per day for three months in rats caused various persistent abnormal behaviors, including hyperactivity, hyperreactivity, eliminated preference for sucrose solution, changes in PFC neurons (103), and changes in social behavior that continued for four months after discontinuation of LSD (33,103).

At the molecular level, LSD has been shown to alter the expression of proteins and genes involved in schizophrenia. In fact, LSD increases mRNA expression for the NMDA receptor subunit NR2A, growth factors Bdnf and Krox20, and GABA-A ion channels (Gabrb1). LSD reduces the expression of RNA for the dopamine receptor gene Drd2, reduces the two subunits in the IV zone of the genes (Cox7a2, Cox8a) of cytochrome C oxidase, as well as reduces the expression of genes (Gstt2, Gstp2) for glutathione glutathione S-transferases (103).

People

LSD effects have been studied in well-controlled studies, usually with fixed single doses, taking into account various parameters such as pharmacokinetic and pharmacodynamic parameters described above; changes in psyche and brain function. Various established tools such as psychic tests, such as the Minnesota Multiphasic Personality Inventory (MMPI), the Scale for Changing Altered State of Consciousness (5D-ASC), the Mystic Experience Questionnaire (MEQ), and magnetic resonance imaging (MRI), are most commonly used for assessment, as well as electromagnetic encephalography (EME), PET positron emission tomography, EEG and other methods. These experiments clearly prove that the changes are different depending on the dose of LSD, both in terms of psychotic experiences and in terms of brain activity (33,42,101-116).

There are no long-term controlled studies with healthy individuals to assess changes in their behavior after repeated use of LSD, which is explained by the fact that it is a drug that is taken from time to time and is not considered addictive.

A controlled study in 2016 analyzed brain activity during the period of dosed use of LSD and in the period thereafter by MRI and magnetoencephalography, the researchers measured blood flow, functional connections within and between the brain networks and brain waves (33,117). Studies show that the acute application of LSD significantly reduces the functional connectivity in the visual, sensorimotor and auditory networks and the default network. On the other hand, they found an increased connection between the networks of subcortical (thalamus, striatum) and cortical (precuneus, anterior cingulate cortex) structures (117). The mystical experiences themselves, according to researchers, are due to the influence of LSD on the visual cortex. They report a reduction in signaling between the parahypocampus and the retrosplenial cortex (RSC), and the magnitude of the reduction correlates with the subjective assessment of „ego dissolution" and „altered meaning." Both conditions are considered hallmarks of psychosis (33).

Genetic Research

Studies with volunteers taking LSD show that the risk of developing psychosis is more pronounced in people with a genetic predisposition to schizophrenia. Eighteen out of 20 relatives of schizophrenics develop psychosis (118,119).

Controlled studies among healthy volunteers and psychiatric patients showed that psychotic reactions after taking LSD in the group of healthy individuals were 0.8/1000 in frequency, lasted 48 hours, and were not associated with suicide attempts. Compared with patients with psychiatric diagnoses, the incidence of psychosis was 1.8/1000 and suicide attempts - 0.4/1000 (69,120).

CLINICAL COURSE OF ACUTE INTOXICATION IN HUMANS

LSD causes distortions of perception in humans and physiological changes. The effects of the experience are called a trip. The intensity of the effects of LSD lasts from 6 to 12 hours depending on the dose, tolerance to the drug, weight and age of the person. They consist of a change in the psyche and autonomic reactions.

Pseudohallucinations

Changes in the psyche include different visual perceptions, different perceptions of time, touch, smell, hearing, as well as different sensations of body movement and spatial perception of one's own body. More often, the person with LSD intoxication identifies these changes in perceptions as unreal events,

realizes their illusory nature, therefore they can be considered as pseudohallucinations.

At low doses, the following experiences are described: rapid change of emotions (euphoria, happiness, fear, anger, laughter, irritation); enhancing the sense of music, change in the sense of time; experiencing a feeling of liberation from the shackles of the ego and reality; opening the consciousness to supernatural experiences; merge with other objects or people; passage of consciousness through different, sometimes shocking dimensions of creation; emergence of memories from the period before birth, access to ancestral memory and the collective unconscious; sense of the ability to reprogram neural connections in the brain; sense of nirvana, samadhi (enlightenment, quantum awakening) (121).

At medium doses, changes in perception of time and space, color hallucinations, merging objects, ego release may be observed. It is claimed that this property of the substance is valuable for psychotherapists. In a state of „dissolving the ego", the inhibitions disappear and it is possible for a large amount of unconscious soul contents to be pushed to the consciousness.

Mystical Experiences

One of the main effects of LSD is the mystical experience and experience of the „transcendence of time and space," which means that one feels beyond the past, present, and future and beyond ordinary three-dimensional space, into the realm of eternity or infinity.

Especially at high doses, „dissolution, disappearance of the boundaries of consciousness and merging of the person with the surrounding world" and other mystical and religious experiences occur (123). Proponents of LSD often mention that it takes several days to prepare for the „journey" into the world of LSD, careful dosing to get the most out of the experience.

Hallucinations

Rare are the cases of real hallucinations in which the intoxicated ones perceive the changes as completely real. Hallucinations usually last between 8 and 15 hours. They are called a „bad trip" if there is a stream of threatening hallucinations that one considers real and over which there is no control. This causes panic and fear, especially of going crazy.

Other possible effects on the central nervous system (CNS) include depersonalization, decreased ability to think and judge, changes in mood and behavior. Patients are usually quiet and withdrawn. Cases of aggression and bizarre behavior have been described. Acute panic attacks are possible, especially with unexpected use and less user experience. Acute psychotic reactions may also occur. Although suicides are rare, the frequency is 0.4/1000 people using LSD (69,120).

Physiological Effects

Physical examination of people taking LSD reveals symptoms characteristic of the so-called serotonin toxin syndrome during the trip: increased systolic and diastolic blood pressure, tachycardia, hyperthermia, sweating, increased muscle tension, muscle incoordination and convulsions (89-91). There is increased salivation, profuse sweating, nausea, dizziness, lightheadedness, coughing in some people, triggering of the sucking reflex or tension in the jaws. Unusual bodily sensations such as reddening of the face, chills, influx of physical energy and sharpening of the senses (taste, sight, smell, touch) are also observed (125).

At high doses, intoxications may occur with severe serotonin syndrome, characterized by hyperreflexia, tremor, mydriasis or anisocoria, hyperthermia, hypertension, seizures, rhabdomyolysis, and coma.

Death

Fatalities have been reported with the use of ergoalkaloids / poisonous fungus *Claviceps purpurea*. The synthetic variant, LSD, is considered safe at doses between 50 and 200 μg. There have been reports of people taking high doses during psychotic experiences under the influence of LSD and suicide, apparently due to threatening hallucinations. Death due to cardiovascular collapse and extreme hyperthermia (18,91,127,128) has also been reported.

Use by Pregnant Women

LSD can cause chromosomal aberrations and an increased risk of congenital anomalies in the fetus when used during pregnancy (92).

New Design Compounds

Several LSD derivatives are known, e.g. designer drugs based on the molecule of diethylamide of lysergin sykeline 1-acetyl-LSD (ALD-52), 1-propionyl-

LSD (1PLSD), and 1-butyryl-LSD (1B-LSD). They are metabolized to LSD in the body and have similar effects (129-133).

CHRONIC USE (ABUSE)

LSD may be abused but it is not thought to lead to physical dependence. It is very important to realize that addiction and physical dependence are different phenomena with different main substrates of the brain.

Addiction (abuse) is a chronically progressive disease characterized by compulsive drug use, combined with loss of control and persistent desire for the drug. Physical dependence is a result of the development of pharmacological tolerance to the drug and the onset of withdrawal after abrupt cessation of intake (135,136). Most authors accept that LSD is taken from time to time for entertainment and is not addictive, but clinical observations show that a large proportion of users take LSD for a long time. The consequences of chronic LSD intake can be unpredictable and can have long-term psycho-emotional effects - both positive and negative. Some people who use LSD claim that the effects are very important for their lives and this has helped them look at their lives from a different angle (13,21,29).

Toxic Effects of LSD in Chronic Use

Due to the presence of individual sensitivity to LSD, toxic manifestations of the drug are considered to affect only „vulnerable people" and „at high doses" and include: /1/ development of so-called „reverse changes in the CNS" in 15 to 77% of users; /2/ permanent hallucinogenic psychosis in about 1%, and /3/ trigger of schizophrenia, rarely.

/1/ Sudden reversal of changes in the CNS, similar to acute intoxication, e.g. „flashes"

With repeated use of LSD, there is a possibility of remembering long-forgotten memories or the so-called „free trip".These are short, but sometimes very intense flashes of pictures, sounds or emotions - pleasant or unpleasant. This psychological phenomenon has not yet been fully scientifically explained. The experiences are identical to those described in the acute use of LSD. Such reverse psychotic changes were observed up to 4 years after the last use of LSD. Reverse changes in the CNS occur in 15-77% of individuals who use LSD and may completely resemble acute intoxication. The return of the mental and physiological manifestations of acute intoxications, after a period of cessation, are provoked mainly by various stressful conditions /mental trauma and post-traumatic stressful conditions/.

/2/ Hallucinogen persisting perception disorder (HPPD)

With repeated abuse of LSD at an average dose of 100-200 μg per os, cases of psychosis are also possible – in approx. 1% of people in the United States using LSD (120,124). Psychosis is described as panic, paranoia and mistrust, metamorphic changes in body contours, changes in body image and intense visual images with transformative content, the appearance of suspicious feelings or delusions of greatness, confusion, disturbance of thought, hallucinations, lack of will or apathy, catatonic motor behavior, disorganized behavior, regret, depression, loneliness, and/or somatic discomfort, all of which can be monumental in size (137). Depending on the psychotic content, delusions are classified as persecutory, grandiose, erotic, nihilistic, or somatic. Other symptoms of LSD-specific psychosis are religious delusions and/or pathological hyperreligiousness (138-140).

/3/ Unlocking schizophrenia

Psychiatrists initially looked for a substance in the brain, similar to LSD, that causes schizophrenia, called „schizotoxin." It is now accepted that the use of LSD does not cause schizophrenia, but substance abuse can trigger pre-existing latent schizophrenia. The risk is also high in people with parents or relatives with schizophrenia (119,142-145). Schizophrenia is diagnosed when the psychotic symptoms last for at least six months and include at least one month of active psychosis. In LSD-induced schizophrenia, some symptoms are assessed as positive, such as hallucinations, delusions, illusions, and disorganized thinking, while others are assessed as negative symptoms, such as emotional withdrawal and apathetic social behavior (146).

CONCLUSION

The interest in LSD is due to the fact that as a drug, its recreational use in Bulgaria is growing, which raises legal, social and toxicological problems that we as experts must answer. On the other hand, it is also available as a medicine for addicted patients and mental disorders. Therefore, the history of use,

its pharmacokinetics and pharmacodynamics, the known acute and chronic toxic effects are considered in detail.

For several years in the United States and some European countries, the method of „reprogramming" or so on has been gaining popularity, e.g. translational psychedelic biomedicine for patients in which serotonergic psychedelics, such as LSD, are used as an alternative approach to treating mood disorders, anxiety, depression, tobacco addiction, cannabis, stimulants, opiates and alcohol. Theoretically, the method consists of acute destabilization of the cerebral network followed by its recovery and improvement of synaptic plasticity. It is therefore important to summarize the published results of preclinical and clinical pilot studies with LSD and the fact that no study to date has shown sufficient efficacy.

In addition, it is important to clarify all the toxic effects of LSD in acute and chronic use, especially by shedding light on the routes of administration, the variability of doses in commercially available forms. The completeness of this information gives us reason to soberly assess the dangers of using the drug LSD and carefully follow the evidence from the proposed experimental approaches with LSD in the treatment of a number of diseases affecting brain neurotransmitters, receptors and synaptic networks.

REFERENCES

1. Ergot of Rye - I: Introduction and History. Botany Department. University of Hawai'i at Mānoa. Avaiable from: http://www.botany.hawaii.edu/faculty/wong/BOT135/LECT12.HTM
2. Nicholson P. The hights and lows of ergot 2015 (2). Available from: https://microbiologysociety.org/publication/past-issues/mind-altering-microbes/article/the-highs-and-lows-of-ergot.html
3. Caporael LR. Ergotism: the Satan loosed in Salem?. Science. 1976;192(4234):21-6. doi:10.1126/science.769159
4. Hofmann A. LSD, My Problem Child. New York, USA: McGraw-Hill; 1980.
5. Oram M. Prohibited or regulated? LSD psychotherapy and the United States Food and Drug Administration. Hist Psychiatry. 2016;27(3):290-306. doi:10.1177/0957154X16648822.
6. Leary T. Available from: https://en.wikipedia.org/wiki/Timothy_Leary
7. Stanislav Grof. Available from: https://bg.wikipedia.org/wiki/%D0%A1%D1%82%D0%B0%D0%BD%D0%B8%D1%81%D0%BB%D0%B0%D0%B2_%D0%93%D1%80%D0%BE%D1%84
8. Smith DE. The role of the Journal of Psychedelic Drugs in the evolution of psychedelic medicine. J Psychoactive Drugs. 2019;51(2):98-101. doi: 10.1080/02791072.2019.1589607.
9. Grunenberg Ch, Harris J. Summer of love: Psychedelic art, social crisis and counterculture in the 1960s. Liverpool University Press; 2005.
10. Smith DE, Raswyck GE, Davidson LD. From Hofmann to the Haight Ashbury, and into the future: the past and potential of lysergic acid diethlyamide. J Psychoactive Drugs. 2014;46(1):3-10. doi:10.1080/02791072.2014.873684.
11. Nichols DE, Johnson MW, Nichols CD. Psychedelics as medicines: An emerging new paradigm. Clin Pharmacol Ther. 2017;101(2):209-19. doi:10.1002/cpt.557.
12. Canal CE. Serotonergic psychedelics: Experimental approaches for assessing mechanisms of action. Handb Exp Pharmacol. 2018;252:227-60. doi:10.1007/164_2018_107777.
13. Dos Santos RG, Osório FL, Crippa JA, Riba J, Zuardi AW, Hallak JE. Antidepressive, anxiolytic, and antiaddictive effects of ayahuasca, psilocybin and lysergic acid diethylamide (LSD): a systematic review of clinical trials published in the last 25 years. Ther Adv Psychopharmacol. 2016;6(3):193-213. doi:10.1177/2045125316638008.
14. Gasser P, Holstein D, Michel Y, Doblin R, Yazar-Klosinski B, Passie T, et al. Safety and efficacy of lysergic acid diethylamide-assisted psychotherapy for anxiety associated with life-threatening diseases. J Nerv Ment Dis. 2014;202(7):513-20. Doi: 10.1097/nmd.0000000000000113.
15. Kyzar EJ, Nichols CD, Gainetdinov RR, Nichols DE, Kalueff AV. Psychedelic drugs in biomedicine. Trends Pharmacol Sci. 2017;38(11):992-1005. doi:10.1016/j.tips.2017.08.003.
16. Bogenschutz MP, Ross S. Therapeutic applications of classic hallucinogens. Curr Top Behav Neurosci. 2018;36:361-91. doi:10.1007/7854_2016_464.
17. Dolder PC, Schmid Y, Müller F, Borgwardt S, Liechti ME. LSD acutely impairs fear recognition and enhances emotional empathy and sociality. Neuropsychopharmacology. 2016;41(11):2638-46. doi:10.1038/npp.2016.82.

18. Mangini M. Treatment of alcoholism using psychedelic drugs: a review of the program of research. J Psychoactive Drugs. 1998;30(4):381-418. doi:10.1080/02791072.1998.10399714.

19. Johnson MW, Garcia-Romeu A, Johnson PS, Griffiths RR. An online survey of tobacco smoking cessation associated with naturalistic psychedelic use. J Psychopharmacol. 2017;31(7):841-50. doi:10.1177/0269881116684335.

20. Bayat M. Classic psychedelic drugs and their potential therapeutic effect. Ugeskr Laeger. 2017;179(37):V01170005.

21. De Gregorio D, Enns JP, Nuñez NA, Posa L, Gobbi G. d-Lysergic acid diethylamide, psilocybin, and other classic hallucinogens: Mechanism of action and potential therapeutic applications in mood disorders. Prog Brain Res. 2018;242:69-96. doi:10.1016/bs.pbr.2018.07.008.

22. Tófoli LF, de Araujo DB. Treating addiction: Perspectives from EEG and imaging studies on psychedelics. Int Rev Neurobiol. 2016;129:157-85. doi:10.1016/bs.irn.2016.06.005.

23. Rickli A, Luethi D, Reinisch J, Buchy D, Hoener MC, Liechti ME. Receptor interaction profiles of novel N-2-methoxybenzyl (NBOMe) derivatives of 2,5-dimethoxy-substituted phenethylamines (2C drugs). Neuropharmacology. 2015;99:546-53. doi:10.1016/j.neuropharm.2015.08.034

24. Martin DA, Nichols CD. The effects of hallucinogens on gene expression. Curr Top Behav Neurosci. 2018;36:137-58. doi:10.1007/7854_2017_479.

25. Dakic V, Minardi Nascimento J, Costa Sartore R, Maciel RM, de Araujo DB, Ribeiro S, et al. Short term changes in the proteome of human cerebral organoids induced by 5-MeO-DMT. Sci Rep. 2017;7(1):12863. doi:10.1038/s41598-017-12779-5

26. Krebs TS, Johansen PØ. Lysergic acid diethylamide (LSD) for alcoholism: meta-analysis of randomized controlled trials. J Psychopharmacol. 2012;26(7):994-1002. doi:10.1177/0269881112439253.

27. Garcia-Romeu A, Davis AK, Erowid F, Erowid E, Griffiths RR, Johnson MW. Cessation and reduction in alcohol consumption and misuse after psychedelic use. J Psychopharmacol. 2019;33(9):1088-101. doi:10.1177/0269881119845793.

28. Dolder PC, Schmid Y, Steuer AE, Kraemer T, Rentsch KM, Hammann F, et al. Pharmacokinetics and pharmacodynamics of lysergic acid diethylamide in healthy subjects. Clin Pharmacokinet. 2017;56(10):1219-30. doi:10.1007/s40262-017-0513-9

29. Dolder PC, Schmid Y, Haschke M, Rentsch KM, Liechti ME. Pharmacokinetics and concentration-effect relationship of oral LSD in humans [published correction appears in Int J Neuropsychopharmacol. 2016 Apr 27;:]. Int J Neuropsychopharmacol. 2015;19(1):pyv072. doi:10.1093/ijnp/pyv072.

30. Kaelen M, Roseman L, Kahan J, Santos-Ribeiro A, Orban C, Lorenz R, et al. LSD modulates music-induced imagery via changes in parahippocampal connectivity. Eur Neuropsychopharmacol. 2016;26(7):1099-109. doi:10.1016/j.euroneuro.2016.03.018.

31. Carhart-Harris RL, Muthukumaraswamy S, Roseman L, Kaelen M, Droog W, Murphy K, et al. Neural correlates of the LSD experience revealed by multimodal neuroimaging. Proc Natl Acad Sci U S A. 2016;113(17):4853-8. doi:10.1073/pnas.1518377113.

32. Roseman L, Sereno MI, Leech R, Kaelen M, Orban C, McGonigle J, et al. LSD alters eyes-closed functional connectivity within the early visual cortex in a retinotopic fashion. Hum Brain Mapp. 2016;37(8):3031-40. doi:10.1002/hbm.23224.

33. Lebedev AV, Kaelen M, Lövdén M, Nilsson J, Feilding A, Nutt DJ, et al. LSD-induced entropic brain activity predicts subsequent personality change. Hum Brain Mapp. 2016;37(9):3203-13. doi:10.1002/hbm.23234.

34. Libânio Osório Marta RF. Metabolism of lysergic acid diethylamide (LSD): an update. Drug Metab Rev. 2019;51(3):378-87. doi:10.1080/03602532.2019.1638931.

35. Luethi D, Hoener MC, Krähenbühl S, Liechti ME, Duthaler U. Cytochrome P450 enzymes contribute to the metabolism of LSD to nor-LSD and 2-oxo-3-hydroxy-LSD: Implications for clinical LSD use. Biochem Pharmacol. 2019;164:129-38. doi:10.1016/j.bcp.2019.04.013.

36. Klette KL, Anderson CJ, Poch GK, Nimrod AC, ElSohly MA. Metabolism of lysergic acid diethylamide (LSD) to 2-oxo-3-hydroxy LSD (O-H-LSD) in human liver microsomes and cryopreserved human hepatocytes. J Anal Toxicol. 2000;24(7):550-6. doi:10.1093/jat/24.7.550.

37. Upshall DG, Wailling DG. The determination of LSD in human plasma following oral ad-

ministration. Clin Chim Acta. 1972;36(1):67-73. doi:10.1016/0009-8981(72)90159-3.

38. Aghajanian GK, Bing OH. Persistence of lysergic acid diethylamide in the plasma of human subjects. Clin Pharmacol Ther. 1964;5:611-4. doi:10.1002/cpt196455611.

39. Liechti M, Dolder P, Schmid Y. Alterations of consciousness and mystical-type experiences after acute LSD in humans. Psychopharmacology (Berl). 2017; 234(9-10):1499–510. doi: 10.1007/s00213-016-4453-0.

40. De Gregorio D, Comai S, Posa L, Gobbi G. d-Lysergic Acid Diethylamide (LSD) as a Model of Psychosis: Mechanism of Action and Pharmacology. Int J Mol Sci. 2016;17(11):1953. doi:10.3390/ijms17111953.

41. Teitler M, Leonhardt S, Appel NM, De Souza EB, Glennon RA. Receptor pharmacology of MDMA and related hallucinogens. Ann N Y Acad Sci. 1990;600:626-39. doi:10.1111/j.1749-6632.1990.tb16915.x.

42. Nichols DE, Frescas S, Marona-Lewicka D, Huang X, Roth BL, Gudelsky GA, et al. 1-(2,5-Dimethoxy-4-(trifluoromethyl)phenyl)-2-aminopropane: a potent serotonin 5-HT2A/2C agonist. J Med Chem. 1994;37(25):4346-51. doi:10.1021/jm00051a011.

43. Geyer MA, Krebs KM. Serotonin receptor involvement in an animal model of the acute effects of hallucinogens. NIDA Res Monogr. 1994. 46:124-56.

44. Halberstadt AL. Recent advances in the neuropsychopharmacology of serotonergic hallucinogens. Behav Brain Res. 2015;277:99-120. doi:10.1016/j.bbr.2014.07.016.

45. Marek GJ, Aghajanian GK. LSD and the phenethylamine hallucinogen DOI are potent partial agonists at 5-HT2A receptors on interneurons in rat piriform cortex. J Pharmacol Exp Ther. 1996;278(3):1373-82.

46. Sanders-Bush E, Breeding M. Choroid plexus epithelial cells in primary culture: a model of $5HT_{1C}$ receptor activation by hallucinogenic drugs. Psychopharmacology (Berl). 1991;105(3):340-6. doi: 10.1007/BF02244428.

47. Egan CT, Herrick-Davis K, Miller K, Glennon RA, Teitler M. Agonist activity of LSD and lisuride at cloned 5HT2A and 5HT2C receptors. Psychopharmacology (Berl). 1998;136(4):409-14. doi:10.1007/s002130050585.

48. López-Giménez JF, González-Maeso J. Hallucinogens and serotonin $5\text{-}HT_{2A}$ receptor-mediated signaling pathways. Curr Top Behav Neurosci. 2018;36:45-73. doi:10.1007/7854_2017_478.

49. Kapur S, Remington G. Serotonin-dopamine interaction and its relevance to schizophrenia. Am J Psychiatry. 1996;153(4):466-76. doi:10.1176/ajp.153.4.466.

50. Rickli A, Moning OD, Hoener MC, Liechti ME. Receptor interaction profiles of novel psychoactive tryptamines compared with classic hallucinogens. Eur Neuropsychopharmacol. 2016;26(8):1327-37. doi:10.1016/j.euroneuro.2016.05.001.

51. Araújo AM, Carvalho F, Bastos Mde L, Guedes de Pinho P, Carvalho M. The hallucinogenic world of tryptamines: an updated review. Arch Toxicol. 2015;89(8):1151-73. doi:10.1007/s00204-015-1513-x.

52. Burt DR, Creese I, Snyder SH. Binding interactions of lysergic acid diethylamide and related agents with dopamine receptors in the brain. Mol Pharmacol. 1976;12(4):631-8.

53. Seeman P, Ko F, Tallerico T. Dopamine receptor contribution to the action of PCP, LSD and ketamine psychotomimetics. Mol Psychiatry. 2005;10(9):877-83. doi:10.1038/sj.mp.4001682.

54. Minuzzi L, Nomikos GG, Wade MR, Jensen SB, Olsen AK, Cumming P. Interaction between LSD and dopamine D2/3 binding sites in pig brain. Synapse. 2005;56(4):198-204. doi:10.1002/syn.20141.

55. Seeman P, Guan HC, Hirbec H. Dopamine D2High receptors stimulated by phencyclidines, lysergic acid diethylamide, salvinorin A, and modafinil. Synapse. 2009;63(8):698-704. doi:10.1002/syn.20647.

56. Watts VJ, Lawler CP, Fox DR, Neve KA, Nichols DE, Mailman RB. LSD and structural analogs: pharmacological evaluation at D1 dopamine receptors. Psychopharmacology (Berl). 1995;118(4):401-9. doi:10.1007/BF02245940.

57. Marona-Lewicka D, Chemel BR, Nichols DE. Dopamine D4 receptor involvement in the discriminative stimulus effects in rats of LSD, but not the phenethylamine hallucinogen DOI. Psychopharmacology (Berl). 2009;203(2):265-77. doi: 10.1007/s00213-008-1238-0.

58. Bunzow JR, Sonders MS, Arttamangkul S, Harrison LM, Zhang G, Quigley DI, et al. Amphetamine, 3,4-methylenedioxymethamphetamine, lysergic acid diethylamide, and metabolites of the catecholamine neurotransmitters are agonists of a rat trace

amine receptor. Mol Pharmacol. 2001;60(6):1181-8. doi:10.1124/mol.60.6.1181.

59. Lindemann L, Meyer CA, Jeanneau K, Bradaia A, Ozmen L, Bluethmann H, et al. Trace amine-associated receptor 1 modulates dopaminergic activity. J Pharmacol Exp Ther. 2008;324(3):948-56. doi:10.1124/jpet.107.132647.

60. Xie Z, Miller GM. Trace amine-associated receptor 1 is a modulator of the dopamine transporter. J Pharmacol Exp Ther. 2007;321(1):128-36. doi:10.1124/jpet.106.117382.

61. Revel FG, Moreau JL, Gainetdinov RR, Bradaia A, Sotnikova TD, Mory R, et al. TAAR1 activation modulates monoaminergic neurotransmission, preventing hyperdopaminergic and hypoglutamatergic activity. Proc Natl Acad Sci U S A. 2011;108(20):8485-90. doi:10.1073/pnas.1103029108.

62. Grandy DK. Trace amine-associated receptor 1-Family archetype or iconoclast? Pharmacol Ther. 2007;116(3):355-90. doi:10.1016/j.pharmthera.2007.06.007.

63. Lindemann L, Hoener MC. A renaissance in trace amines inspired by a novel GPCR family. Trends Pharmacol Sci. 2005;26(5):274-81. doi:10.1016/j.tips.2005.03.007.

64. Miller GM. The emerging role of trace amine-associated receptor 1 in the functional regulation of monoamine transporters and dopaminergic activity. J Neurochem. 2011;116(2):164-76. doi:10.1111/j.1471-4159.2010.07109.x.

65. Narang D, Tomlinson S, Holt A, Mousseau DD, Baker GB. Trace amines and their relevance to psychiatry and neurology: A brief overview. Bull Clin Psychopharmacol. 2011;21:73–9.

66. Johansen PØ, Krebs TS. Psychedelics not linked to mental health problems or suicidal behavior: a population study. J Psychopharmacol. 2015;29(3):270-9. doi:10.1177/0269881114568039.

67. Zimmermann G, Favrod J, Trieu VH, Pomini V. The effect of cognitive behavioral treatment on the positive symptoms of schizophrenia spectrum disorders: a meta-analysis. Schizophr Res. 2005;77(1):1-9. doi:10.1016/j.schres.2005.02.018.

68. Kringelbach ML, Berridge KC. Towards a functional neuroanatomy of pleasure and happiness. Trends Cogn Sci. 2009;13(11):479-87. doi:10.1016/j.tics.2009.08.006.

69. Farde L, Nordström AL, Wiesel FA, Pauli S, Halldin C, Sedvall G. Positron emission tomographic analysis of central D1 and D2 dopamine receptor occupancy in patients treated with classical neuroleptics and clozapine. Relation to extrapyramidal side effects. Arch Gen Psychiatry. 1992;49(7):538-44. doi:10.1001/archpsyc.1992.01820070032005.

70. Nordström AL, Farde L. Plasma prolactin and central D2 receptor occupancy in antipsychotic drug-treated patients. J Clin Psychopharmacol. 1998;18(4):305-10. doi:10.1097/00004714-199808000-00010.

71. Kapur S, Remington G. Serotonin-dopamine interaction and its relevance to schizophrenia. Am J Psychiatry. 1996;153(4):466-76. doi:10.1176/ajp.153.4.466.

72. Davis KL, Kahn RS, Ko G, Davidson M. Dopamine in schizophrenia: a review and reconceptualization. Am J Psychiatry. 1991;148(11):1474-86. doi:10.1176/ajp.148.11.1474.

73. Berry MD. The potential of trace amines and their receptors for treating neurological and psychiatric diseases. Rev Recent Clin Trials. 2007;2(1):3-19. doi:10.2174/157488707779318107.

74. Sotnikova TD, Caron MG, Gainetdinov RR. Trace amine-associated receptors as emerging therapeutic targets. Mol Pharmacol. 2009;76(2):229-35. doi:10.1124/mol.109.055970.

75. Meltzer HY, Massey BW. The role of serotonin receptors in the action of atypical antipsychotic drugs. Curr Opin Pharmacol. 2011;11(1):59-67. doi:10.1016/j.coph.2011.02.007.

76. Burchett SA, Hicks TP. The mysterious trace amines: protean neuromodulators of synaptic transmission in mammalian brain. Prog Neurobiol. 2006;79(5-6):223-46. doi:10.1016/j.pneurobio.2006.07.003.

77. De Gregorio D, Posa L, Ochoa-Sanchez R, McLaughlin R, Maione S, Comai S, et al. The hallucinogen d-lysergic diethylamide (LSD) decreases dopamine firing activity through 5-HT_{1A}, D_2 and $TAAR_1$ receptors. Pharmacol Res. 2016;113(Pt A):81-91. doi:10.1016/j.phrs.2016.08.022.

78. Pehek EA, Nocjar C, Roth BL, Byrd TA, Mabrouk OS. Evidence for the preferential involvement of 5-HT2A serotonin receptors in stress- and drug-induced dopamine release in the rat medi-

al prefrontal cortex. Neuropsychopharmacology. 2006;31(2):265-77. doi:10.1038/sj.npp.1300819.

79. Shah UH, González-Maeso J. Serotonin and Glutamate Interactions in Preclinical Schizophrenia Models. ACS Chem Neurosci. 2019;10(7):3068-77. doi:10.1021/acschemneuro.9b00044.

80. Aghajanian GK, Marek GJ. Serotonin model of schizophrenia: emerging role of glutamate mechanisms. Brain Res Brain Res Rev. 2000;31(2-3):302-12. doi:10.1016/s0165-0173(99)00046-6.

81. Lambe EK, Aghajanian GK. Hallucinogen-induced UP states in the brain slice of rat prefrontal cortex: role of glutamate spillover and NR2B-NMDA receptors. Neuropsychopharmacology. 2006;31(8):1682-9. doi:10.1038/sj.npp.1300944.

82. Chandler DJ, Lamperski CS, Waterhouse BD. Identification and distribution of projections from monoaminergic and cholinergic nuclei to functionally differentiated subregions of prefrontal cortex. Brain Res. 2013;1522:38-58. doi:10.1016/j.brainres.2013.04.057.

83. Arvanov VL, Liang X, Russo A, Wang RY. LSD and DOB: interaction with 5-HT2A receptors to inhibit NMDA receptor-mediated transmission in the rat prefrontal cortex. Eur J Neurosci. 1999;11(9):3064-72. doi:10.1046/j.1460-9568.1999.00726.x.

84. Steketee JD. Neurotransmitter systems of the medial prefrontal cortex: potential role in sensitization to psychostimulants. Brain Res Brain Res Rev. 2003;41(2-3):203-28. doi:10.1016/s0165-0173(02)00233-3.

85. Rickli A, Moning OD, Hoener MC, Liechti ME. Receptor interaction profiles of novel psychoactive tryptamines compared with classic hallucinogens. Eur Neuropsychopharmacol. 2016;26(8):1327-37. doi:10.1016/j.euroneuro.2016.05.001.

86. Goodman N. The serotonergic system and mysticism: could LSD and the nondrug-induced mystical experience share common neural mechanisms? J Psychoactive Drugs. 2002;34(3):263-72. doi:10.1080/02791072.2002.10399962.

87. Dawson P, Moffatt JD. Cardiovascular toxicity of novel psychoactive drugs: lessons from the past. Prog Neuropsychopharmacol Biol Psychiatry. 2012;39(2):244-52. doi:10.1016/j.pnpbp.2012.05.003.

88. Schmid Y, Enzler F, Gasser P, Grouzmann E, Preller KH, Vollenweider FX, et al. Acute effects of lysergic acid diethylamide in healthy subjects. Biol Psychiatry. 2015;78(8):544-53. doi:10.1016/j.biopsych.2014.11.015.

89. Wexler P. Encyclopedia of Toxicology. Vol. 2. Academic Press, USA; 2014. p. 750-2.

90. Rickli A, Luethi D, Reinisch J, Buchy D, Hoener MC, Liechti ME. Receptor interaction profiles of novel N-2-methoxybenzyl (NBOMe) derivatives of 2,5-dimethoxy-substituted phenethylamines (2C drugs). Neuropharmacology. 2015;99:546-53. doi:10.1016/j.neuropharm.2015.08.034.

91. Giacomelli S, Palmery M, Romanelli L, Cheng CY, Silvestrini B. Lysergic acid diethylamide (LSD) is a partial agonist of D2 dopaminergic receptors and it potentiates dopamine-mediated prolactin secretion in lactotrophs in vitro. Life Sci. 1998;63(3):215-22. doi:10.1016/s0024-3205(98)00262-8.

92. Hoch PH. Experimentally produced psychoses. Am J Psychiatry. 1951; 107:607–11.

93. Marona-Lewicka D, Nichols CD, Nichols DE. An animal model of schizophrenia based on chronic LSD administration: old idea, new results. Neuropharmacology. 2011;61(3):503-12. doi:10.1016/j.neuropharm.2011.02.006.

94. Halberstadt AL, Geyer MA. Serotonergic hallucinogens as translational models relevant to schizophrenia. Int J Neuropsychopharmacol. 2013;16(10):2165-80. doi:10.1017/S1461145713000722.

95. Sanders-Bush E, Burris KD, Knoth K. Lysergic acid diethylamide and 2, 5-dimethoxy-4-methylamphetamine are partial agonists at serotonin receptors linked to phosphoinositide hydrolysis. J Pharmacol Exp Ther. 1988; 246(3):924-8.

96. Reissig CJ, Eckler JR, Rabin RA, Winter JC. The 5-HT1A receptor and the stimulus effects of LSD in the rat. Psychopharmacology (Berl). 2005;182(2):197-204. doi:10.1007/s00213-005-0068-6.

97. Nichols CD, Sanders-Bush E. Molecular genetic responses to lysergic acid diethylamide include transcriptional activation of MAP kinase phosphatase-1, C/EBP-beta and ILAD-1, a novel gene with homology to arrestins. J Neurochem. 2004;90(3):576-84. doi:10.1111/j.1471-4159.2004.02515.x.

98. Marona-Lewicka D, Thisted RA, Nichols DE. Distinct temporal phases in the behavioral pharmacology of LSD: dopamine D2 receptor-mediated effects in the rat and implications for psycho-

sis. Psychopharmacology (Berl). 2005;180(3):427-35. doi:10.1007/s00213-005-2183-9.

99. Marona-Lewicka D, Nichols DE. Further evidence that the delayed temporal dopaminergic effects of LSD are mediated by a mechanism different than the first temporal phase of action. Pharmacol Biochem Behav. 2007;87(4):453-61. doi: 10.1016/j.pbb.2007.06.001.

100. Martin DA, Marona-Lewicka D, Nichols DE, Nichols CD. Chronic LSD alters gene expression profiles in the mPFC relevant to schizophrenia. Neuropharmacology. 2014;83:1-8. doi: 10.1016/j.neuropharm.2014.03.013.

101. Solinas M, Panlilio LV, Justinova Z, Yasar S, Goldberg SR. Using drug-discrimination techniques to study the abuse-related effects of psychoactive drugs in rats. Nat Protoc. 2006;1(3):1194-206. doi:10.1038/nprot.2006.167.

102. Geyer MA, Swerdlow NR, Mansbach RS, Braff DL. Startle response models of sensorimotor gating and habituation deficits in schizophrenia. Brain Res Bull. 1990; 25:485–98.

103. Nichols DE. Psychedelics. Pharmacol Rev. 2016 Apr;68(2):264-355. doi: 10.1124/pr.115.011478.

104. Schneider, K. Clinical psychopathology. New York, NY, USA: Grune & Stratton; 1959. p. 95.

105. Steeds H, Carhart-Harris RL, Stone JM. Drug models of schizophrenia. Ther Adv Psychopharmacol. 2015;5(1):43-58. doi:10.1177/2045125314557797.

106. Woolley D, Shaw E. Some neurophysiological aspects of serotonin. Br Med J. 1954; 2:122–6.

107. Shaw E, Woolley D. Some serotoninlike activities of lysergic acid diethylamide. Science. 1956; 124:121–2.

108. Blacker KH, Jones RT, Stone GC, Pfefferbaum D. Chronic users of LSD: the „acidheads". Am J Psychiatry. 1968;125(3):97-107.

109. McGlothlin W, Arnold DO, Freedman DX. Organicity measures following repeated LSD ingestion. Arch Gen Psychiatry. 1969;21(6):704-9. doi: 10.1001/archpsyc.1969.01740240064008.

110. Abraham HD. A chronic impairment of colour vision in users of LSD. Br J Psychiatry. 1982;140:518-20. doi:10.1192/bjp.140.5.518.

111. Halpern JH, Pope HG Jr. Hallucinogen persisting perception disorder: what do we know after 50 years? Drug Alcohol Depend. 2003;69(2):109-19. doi:10.1016/s0376-8716(02)00306-x.

112. Yanakieva S, Polychroni N, Family N, Williams LTJ, Luke DP, Terhune DB. The effects of microdose LSD on time perception: a randomised, double-blind, placebo-controlled trial. Psychopharmacology (Berl). 2019;236(4):1159-70. doi:10.1007/s00213-018-5119-x.

113. Schmid Y, Liechti ME. Long-lasting subjective effects of LSD in normal subjects. Psychopharmacology (Berl). 2018;235(2):535-45. doi: 10.1007/s00213-017-4733-3.

114. Müller F, Dolder PC, Schmidt A, Liechti ME, Borgwardt S. Altered network hub connectivity after acute LSD administration. Neuroimage Clin. 2018;18:694-701. doi: 10.1016/j.nicl.2018.03.005.

115. Langs RJ, Barr HL. Lysergic acid diethylamide (LSD-25) and schizophrenic reactions. A comparative study. J Nerv Ment Dis. 1968 Aug;147(2):163-72. doi: 10.1097/00005053-196808000-00008.

116. Anastasopoulos G, Photiades H. Effects of LSD-25 on relatives of schizophrenic patients. J Ment Sci. 1962;108:95-8. doi: 10.1192/bjp.108.452.95.

117. Cohen S. Lysergic acid diethylamide: side effects and complications. J Nerv Ment Dis. 1960;130:30-40. doi:10.1097/00005053-196001000-00005.

118. Bower B. Chemical Enlightenment. 2006. Available from: www.sciencenews.org

119. Pahnke WN. LSD and religious experience. LSD man & society. Middletown, CT, USA: Wesleyan University Press; 1967. pp. 60–85.

120. LSD. Available from: https://bg.wikipedia.org/wiki/%D0%9B%D0%A1%D0%94#cite_ref-13. (in Bulgarian).

121. Cohen S. A classification of LSD complications. Psychosomatics. 1966;7(3):182-6. doi:10.1016/S0033-3182(66)72149-5.

122. Borgwardt S, Liechti ME. Acute effects of lysergic acid diethylamide in healthy subjects. Biol Psychiatry. 2015; 78:544–53.

123. Nichols DE, Grob CS. Is LSD toxic? Forensic Sci Int. 2018;284:141-5. doi:10.1016/j.forsciint.2018.01.006.

124. Suzuki J, Poklis JL, Poklis A. „My friend said it was good LSD": a suicide attempt following analytically confirmed 25I-NBOMe ingestion. J Psychoactive Drugs. 2014;46(5):379-82. doi:10.1080/02791072.2014.960111.

125. Grumann C, Henkel K, Stratford A, Hermanns-Clausen M, Passie T, Brandt SD, et al. Validation of

an LC-MS/MS method for the quantitative analysis of 1P-LSD and its tentative metabolite LSD in fortified urine and serum samples including stability tests for 1P-LSD under different storage conditions. J Pharm Biomed Anal. 2019;174:270-6. doi:10.1016/j.jpba.2019.05.062.

126. Coney LD, Maier LJ, Ferris JA, Winstock AR, Barratt MJ. Genie in a blotter: A comparative study of LSD and LSD analogues' effects and user profile. Hum Psychopharmacol. 2017;32(3). doi:10.1002/hup.2599. doi:10.1002/hup.2599.

127. Shulgin A, Shulgin A. PIHKAL: a chemical love story. Transform Press, Berkley; 1995.

128. Shulgin A, Shulgin A. TIHKAL: the continuation. Transform Press, Berkley; 1997.

129. Wagmann L, Brandt SD, Stratford A, Maurer HH, Meyer MR. Interactions of phenethylamine-derived psychoactive substances of the 2C-series with human monoamine oxidases. Drug Test Anal. 2019a; 11(2):318–24. doi:10.1002/dta.2494.

130. Wagmann L, Richter LHJ, Kehl T, Wack F, Bergstrand MP, Brandt SD, et al. In vitro metabolic fate of nine LSD-based new psychoactive substances and their analytical detectability in different urinary screening procedures. Anal Bioanal Chem. 2019b; 411(19):4751–63.

131. Volkow ND, Morales M. The brain on drugs: From reward to addiction. Cell. 2015 Aug 13;162(4):712-25. doi: 10.1016/j.cell.2015.07.046.

132. O'Brien CP, Gardner EL. Critical assessment of how to study addiction and its treatment: human and non-human animal models. Pharmacol Ther. 2005; 108:18-58.

133. Unger S. The current scientific status of psychedelic drug research; unpublished paper read to the Conference on Method in Philosophy and the Sciences in New York City on 3 May 1964. Vol. 3. The University of Edinburgh: Edinburgh, UK; 1964.

134. Hartley S, Barrowclough C, Haddock G. Anxiety and depression in psychosis: A systematic review of associations with positive psychotic symptoms. Acta Psychiatr Scand. 2013; 128:327–46.

135. Faerden A, Barrett EA, Nesvåg R, Friis S, Finset A, Marder SR, et al. Apathy, poor verbal memory and male gender predict lower psychosocial functioning one year after the first treatment of psychosis. Psychiatry Res. 2013;210(1):55-61. doi:10.1016/j.psychres.2013.02.007.

136. Tan N, van Os J. Schizofreniespectrum en andere psychotische stoornissen in de DSM-5 [The schizophrenia spectrum and other psychotic disorders in the DSM-5]. Tijdschr Psychiatr. 2014;56(3):167-72.

137. Osmond H, Smythies J. Schizophrenia: A new approach. Br J Psychiatry. 1952; 98:309–15.

138. Power RA, Verweij KJ, Zuhair M, Montgomery GW, Henders AK, Heath AC, et al. Genetic predisposition to schizophrenia associated with increased use of cannabis. Mol Psychiatry. 2014;19(11):1201-4. doi:10.1038/mp.2014.51.

139. Henquet C, Di Forti M, Morrison P, Kuepper R, Murray RM. Gene-environment interplay between cannabis and psychosis. Schizophr Bull. 2008;34(6):1111-21. doi:10.1093/schbul/sbn108.

140. Vardy MM, Kay SR. LSD psychosis or LSD-induced schizophrenia? A multimethod inquiry. Arch Gen Psychiatry. 1983;40(8):877-83. doi:10.1001/archpsyc.1983.01790070067008.

141. Barrett FS, Bradstreet MP, Leoutsakos JS, Johnson MW, Griffiths RR. The Challenging Experience Questionnaire: Characterization of challenging experiences with psilocybin mushrooms. J Psychopharmacol. 2016;30(12):1279-95. doi:10.1177/0269881116678781.

142. Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr Bull. 1987;13(2):261-76. doi:10.1093/schbul/13.2.261.