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New psychoactive substances in Poland: An overview of psychodysleptics (lysergamides and tryptamines)

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ABSTRACT

New psychoactive substances (NPS) sometimes referred to as “legal highs” or “designer drugs” are psychotropic materials that mimic the effects of other banned illicit drugs but are not always controlled under drug legislation. NPS are typically marketed as “not for human consumption” and are instead labelled and sold as research chemicals in Poland to avoid legislative controls. One of the main NPS classes are hallucinogens. The present paper aims at providing an overview of two groups of psychedelic drugs – lysergamides and tryptamines, and determining their legislation status in Poland. Psychodysleptics have always been of interest to people who want to experiment with their senses and boundaries. They may show beneficial effects which, from a medical point of view indicate the possibility of using them in therapies. NPS that have been described in this paper: 1-Propionyl-*d*-lysergic acid diethylamide (1P-LSD), 6-Allyl-6-nor-lysergic acid diethylamide (AL-LAD), 6-Ethyl-6-nor-lysergic acid diethylamide (ETH-LAD), 4-hydroxy-*N*-methyl-*N*-ethyltryptamine (4-HO-MET), 5-methoxy-*N,N*-diallyltryptamine (5-MeO-DALT).

Keywords: New psychoactive substances, lysergamides, tryptamines, psychedelic therapy, psychodysleptics, hallucinogens, designer drugs

1. INTRODUCTION

New psychoactive substances (NPS) are compounds with psychotropic effects that are distributed for recreational purposes by exploiting inadequacies in existing controlled substance legislation [1].

In contrast to classic illicit drugs novel psychoactive substances are sold through the Internet. The substances are misbranded as “research chemicals” and labelled as “not intended for human consumption, and strictly for laboratory reagent or forensic analysis purposes only”, in an attempt to avoid legal risk, but they are clearly for human consumption. NPS include, among others, synthetic hallucinogens being currently monitored by the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA). This agency gathers information from various national sources including police, customs, forensic laboratory networks, health care systems or event organizers. Internet is also an important method to describe trends in new substances available for online sale [2].

Typically, NPS are derivatives of banned drugs. These analogues are slightly different in their chemical structure but are capable of evoking similar effects. Synthetic drugs are produced in China and Southeast Asia and sold and distributed throughout Europe, including Poland, by online vendors as cheaper alternatives to banned classic drugs [3].

NPS have rarely been studied for the purposes they are being used for and they constitute a potential threat to the health of society. The present paper aims at providing an overview of two groups of psychodysleptic drugs that are novel psychoactive substances currently in use in Poland.

The term "psychodysleptics" is applied interchangeably with "psychedelics" and "hallucinogens". They are psychoactive substances that strongly influence the perception, mood and cognitive processes. Hallucinogens are considered to be physiologically safe, non-addictive. However, their use may lead to unpredictable actions [4].

Serotonergic psychedelics are usually considered to be the classical psychedelics. This group of substances include tryptamines, lysergamides, and certain phenethylamines. Also, due to the vast amount of possible substitutions and analogs of psychedelic compounds, their total number is quite large. This paper discusses lysergamides and tryptamines currently available on the research chemicals market in Poland.

It is believed that psychodysleptics stimulate 5-HT_{2A} receptors, especially those expressed on neocortical pyramidal cells. Activation of 5-HT_{2A} receptors also leads to increased cortical glutamate levels, perhaps by a presynaptic receptor-mediated release from thalamic afferents [5].

Most psychedelic substances have been classified as “drugs of abuse” with no recognized medical value, but recent research indicates that these substances may be useful for treating mental disorders such as obsessive-compulsive disorder, post-traumatic stress disorder, alcoholism, depression and cluster headache [6].

2. METHODS

PubMed was searched for studies indexed or published or both using the following key words alone or in combination: *psychedelics, new psychoactive substances, novel psychoactive substances, legal high, tryptamine, lysergamide, designer drugs, research*

chemicals, hallucinogenic drugs, emerging drugs of abuse, psychedelic therapy. A similar search was conducted for specific substances. After a thorough analysis, 48 documents had finally been considered here as consistent with the aims of the article. Information was also gathered from national Legal Acts.

3. RESULT

3. 1. Legislation status of NPS in Poland

European Monitoring Centre for Drugs and Drug Addiction showed that In 2013 in the EU countries tryptamines represented 2% of total confiscated new psychoactive drugs, whereas phenylethylamines represented 8%. Cannabinoids and cathinones had primacy. As shown in the years 2005-2014, the tendency to use new psychoactive drugs increases and so does their diversity. The proportion of psychoactive drugs in relation to other substances changed as well, in 2005 tryptamines represented about half of new psychoactive substances, whereas in the following years their percentage has significantly decreased.

UR-144, Pente-dron, Etkatynon, Brefedron, 3,4-DMMC, AM-2201, JWH-081, Izo-pentadron, MDPBP, MDPV were most frequently detected substitutive substances in 2012 in Poland. They are included in a group of synthetic cannabinoids, cathinones and phenylethylamine derivatives. The hallucinogen substances such as 2-CE from phenylethylamine group were also identified and so were tryptamine derivatives - 4-HO-MET and 4-AcO-DMT. It is worth mentioning that in 2014 to Distant Early Warning 101 new psychoactive substances were reported, including: 31 cathinones, 30 cannabinoids, 9 phenylethylamines, 5 opioids, 5 triptamines, 4 benzodiazepines, 4 ariloalkiloamines and 13 other substances. According to Central Criminal Laboratory, in the first half of 2014 phenylethylamine derivatives represented 7,64% of legal high groups and tryptamines 0,56%.

Over the years 2015-2016, the organs of the State Sanitary Inspection have identified “legal highs” as single substances or mixtures of many substances in form of powders, dried plants, tablets, ductile masses. Depending on the form, they were swallowed, smoked, snorted, injected into veins or inhaled. In 2015 tryptamines represented 0,04% of new drugs in Poland, 5-MeO-MIPT was the detected substance.

The Act of 29 July 2005 defined a substitutive substance as „a substance in any physical state which is a poison or a harmful substance used instead of or for the same purposes other than medical as an intoxicant or psychotropic substance”.

However, the legislator did not recognize substitutive substances as harmful as other intoxicating substances and no legal restrictions were brought in to prevent their use. The NPS problem was still increasing. Since 2005, store chains so-called “smart shops” offering psychoactive substances have been opened in Europe. In 2008 in Poland there were 50 shops offering “legal highs”, over the years 2009-2010 their number increased to almost 1400.

Experts estimated that about 350 000 people were designer drugs shops customers.

It resulted in a passage of the Act of 8 October 2010 about the change in the Act on Counteracting Drug Addiction and the Act of State Sanitary Inspectorate where new psychoactive substances, their production and trading were defined. The new definition has replaced the old one by defining a designer drug as a natural or synthetic substance in any physical state or a product, plant, fungus or its part containing such a substance, used instead of mind-expanding or psychotropic substance with the same purpose, whose production and

trading is not regulated by individual regulations; substitutive provisions do not apply to the general safety of products. The Act prohibited the production of substitutive substances as well as new psychoactive ones and placing them on the market in the territory of the Republic of Poland.

However, as far as back in 2009, the initial struggle with new psychoactive drugs was initiated by introducing an amendment to the law on counteracting drug addiction. The list of controlled substances was broadened with benzopiperazine, cannabinoid receptors agonist JWH-10 and a dozen of plants. In 2010, another amendment to the Act was introduced, expanding the list of controlled substances with synthetic cannabinoids and a stimulant such as mephedrone. In the amendment of the Act from 2011, other substances were added to the list, such as synthetic cannabinoids (JWH-122, RCS-4, JWH-081), piperazine derivatives (4-fluorophenylpiperazine, MBZP), and also a psychedelic substance from phenylethylamines group 2C-E. As can be seen, synthetic cannabinoids and stimulants dominate amongst listed substances.

On 24 April 2015, many psychedelics were added to the controlled substances list, including those from the phenylethylamine group, such as 25B-NBOMe, 25C-NBOMe, 25I-NBOMe, 2C-P, 2C-C, 2C-N but also tryptamine derivatives, among others 4-HO-DiPT, 4-HO-MET, 5-MeO-DMT, 5-MeO-MiPT, 5-MeO-DALT, 4-AcO-DMT, 4-AcO-MET. A new psychoactive substance was named and defined as „a natural or synthetic substance in any physical state which affects CNS, specified in the regulations issued on the basis of art. 44b act 2.

According to the latest act, a new psychoactive substances is defined as a product containing a substance which affects CNS, which can be used for the same purposes as a narcotic drug, psychotropic substance or a new psychoactive substance whose production and placing on the market is not regulated by individual regulations; substitutive substances do not apply to the general safety of products.

Another attempt in the fight against legal highs is the Act yet to be introduced on 1 November 2018, in which new psychoactive substances will be treated equally to the drugs, and substitutive substances will be covered by a financial penalty until their composition is determined. Penalties up to 3 years will be provided for possession of significant amounts of designer drugs, while traders will be sentenced up to 12 years in prison. The holders of prohibited substances will also be held liable. Additionally, poisoning cases of new psychoactive substance or substitutive substance will be reported to the State Sanitary Inspection. Institutions that suspect the patient of the use of designer drugs will be obligated to inform the district sanitary inspector. After revisions, the process of adding substances on the list of prohibited compounds will be much faster. After the new regulations come into force, lists of prohibited compounds will constitute an attachment to regulations of the Minister of Health, but not to the act, which will significantly accelerate the process of designer drug's. What is important, the list of new psychoactive substances will additionally contain groups of compounds with a specific chemical structure and not only individual substances, so that every analogue can be outlawed due to its chemical structure.

Similar steps were also taken in other countries. In Great Britain, a law was introduced on the basis of which whole groups of compounds with a similar chemical structure are controlled, instead of the delegalization of individual substances [7].

Furthermore, the British law struck especially against online shops. After introducing restrictions on legal highs online shops were closed, some of the domains were moved to the

foreign servers, and some of the shops from outside the country declared that they would no longer ship their products to Great Britain. The aim was to reduce selling and access to legal highs, which somewhat succeeded, however it is hard to control what percentage of sales has moved to the criminal network. Certainly, the regulations coming into force on 1 November 2018 in Poland will further reduce the sales and consumption of legal highs, but the problem will probably not be eliminated. It is confirmed by reports from Ireland, where after the introduction of bans the consumption of legal highs has decreased significantly, however it has not been completely eliminated [8].

Currently in Poland (as of 30/08/2018) psychedelic substances not included in the list of psychotropic substances are among others 4-HO-MiPT belonging to the group of tryptamine derivatives, 1P-LSD, ETH-LAD and AL-LAD belonging to lysergamide analogues.

3. 2. Tryptamines

Tryptamines are hallucinogenic indoloalkylamines (IAA). Structural characteristics of lateral aliphatic chains have an impact on tryptamines activity. The α -methyl group confers resistance to degradation by monoamine oxidase. Moreover it implicates bioavailability after oral use. Due to that fact, α -methyl compounds such as α -methyltryptamine have elongated time of action [9].

The most active α – methyltryptamine and 5-methoxy- α -methyltryptamine's enantiomer is a plus (+) form, which shows how important stereochemical structure is as well. According to studies on rats, IAA acts strongest for 5-HT_{2A} receptors and 2 to 10 times weaker for 5-HT_{2B} receptors. 4-hydroxylated derivatives had 25–380-fold selectivity for the 5-HT_{2A} versus 5-HT_{1A} receptor, but 5-substituted derivatives were equally potent at both 5-HT_{1A} and 5-HT_{2A} receptors. Groups bereft of substitutions in position 4 or 5 showed weaker affinity to all 5-HT receptors [10].

Tryptamine is a basal structural unit for serotonin. IAAs are built of indolic part and alkaline nitrogenous atom connected with alkyl chain containing at least 2 carbon atoms [12].

Tryptamines are organic monoamine compounds. Their structure contains, among others, an indole group composed of a benzene ring and a pyrrole ring connected by a side chain to an amine group. These are derivatives of tryptophan, amino acid, which occurs in the human body (see Figure 1). They act as a neurotransmitter and modulator releasing serotonin and enhancing serotonergic activity [13, 14].

Natural tryptamines include important neurotransmitters such as serotonin and melatonin. They are generally less selective and have lower affinity for the receptor 5-HT_{2A} than hallucinogenic phenylethylamines.

The mechanism of psychoactivity is more complex and many tryptamines are substrates for SERT, VMAT2 or other receptors. Although tryptamines have mainly hallucinogenic properties, some alpha-methylated tryptamines including AMT and 5-MeO-AMT also have stimulant properties, which is associated with the presence of alpha carbon methyl group a feature common with amphetamine. The hallucinogenic activity of these substances is conditioned by the substitution of substitutions.

Both AMT and alpha ethyltryptamine (AET) in addition to hallucinogenic properties also have stimulatory properties. This is due to the fact that they are strong inhibitors of dopamine reuptake, norepinephrine and serotonin which is connected with their neurotoxicity. There is also the risk of serotonin syndrome, as with other drugs that release serotonin.

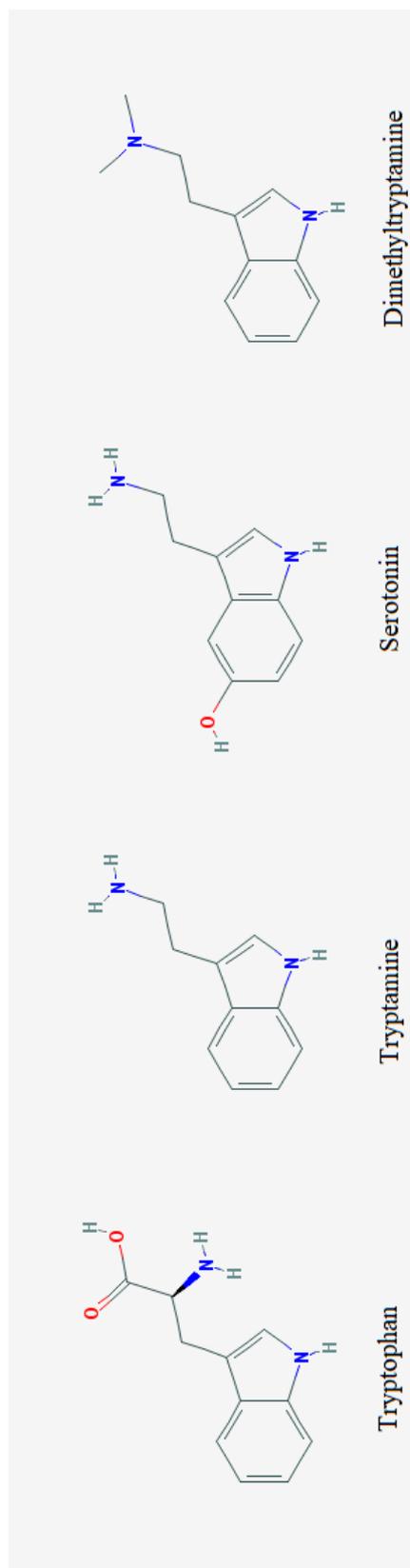


Figure 1. Tryptophan, tryptamine, serotonin and dimethyltryptamine structure [11].

However, tryptamines are generally regarded as not directly life threatening. Large overdose can cause tachycardia, hyperthermia, respiratory depression and CNS depression, hypersensitivity, changes in the sense of time and space, feeling of unreality and depersonalization, and also all states related to psychosis, hallucinations and the resulting behaviors that could be life-threatening. Side effects also include hyperreflexia, ataxia, clonus, paranoia, delusions, confusion, excited delirium, echolalia, severe agitation, anterograde amnesia and catalepsy. The effects depend on the mood and personality of the user as well.

Panic reactions, colloquially known as "bad trips" and also known as "flashbacks", may appear, where panic attacks return after a few days, months or years after taking. Hallucinogens are potent drugs capable of changing perception at doses considered to be harmless to organ system, because they do not have adequate receptors in the kidneys, liver or cardiovascular system, so they do not pose as much danger as other drugs. However, fatal cases of synthetic tryptamines have been reported [11, 14].

The largest amount of information on the pharmacology of simple tryptamines is provided by DMT, derived from natural sources. DMT has putative activity on sigma-1 receptors that are ubiquitous in the central nervous system. The participation of this effect in the hallucinogenic effect is unknown [15].

N-N-dimethyltryptamine (DMT) is naturally present in mammals brains. It is ring-unsubstituted with two methyl groups added to the amino group. It is not active after oral administration because of metabolism, which is why it is used simultaneously with MAO inhibitors in the form of ayahuasca, as well as smoked, injected intravenously or intramuscularly. Ayahuasca called „vine of the soul” is a combination of β -carboline alkaloids (MAO inhibitors) from *Banisteriopsis caapi* and DMT from *Psychotria viridis* [16].

Typical DMT dosage during smoking is about 60000 mg, the onset of action begins within a minute. It takes 10-15 minutes after intramuscular application and up to an hour after oral use. Intensive visual hallucinations and sympathomimetic reactions are the main action effects. It doesn't last long and typically after an hour the effects are over. DALT, DET, DiPT and DPT belong to other unsubstituted simple synthetic triptamines. Each of them makes similar effect to DMT, however DiPT causes mainly auditory hallucinations.

Psilocin (4-hydroxy-N,N-dimethyltryptamine) and psilocybin (4-phosphoryloxy-N,N-dimethyltryptamine) belong to 4-substituted triptamines. They are active ingredients of hallucinogenic Psilocybin mushroom. Typical psilocin dosage is about 6-20mg, the onset of action begins after 20-30 minutes and effects last 4-8 hours.

Psilocin is a partial agonist for 5-HT_{2A} receptors, but it also presents minor dopaminergic and noradrenergic activity. Visual hallucinations dominate, however there is also certain sympathetic component with tachycardia, hypertension and dilated pupils.

4-HO-DET, 4-HO-MiPT, 4-HO-DiPT and their acetic acid derivatives such as 4-AcO-DMT fall into designed synthetic 4-substituted tryptamines category.

5-MeO-DIPT, 5-MeO-MIPT, 5-MeO-DMT fall into 5-substituted tryptamines category.

These compounds prevent the monoamines reuptake, but they have limited impact on their release. They represent similar clinical effects as those with unsubstituted molecule, however they act stronger, which is somewhat connected to their greater toxicity [14].

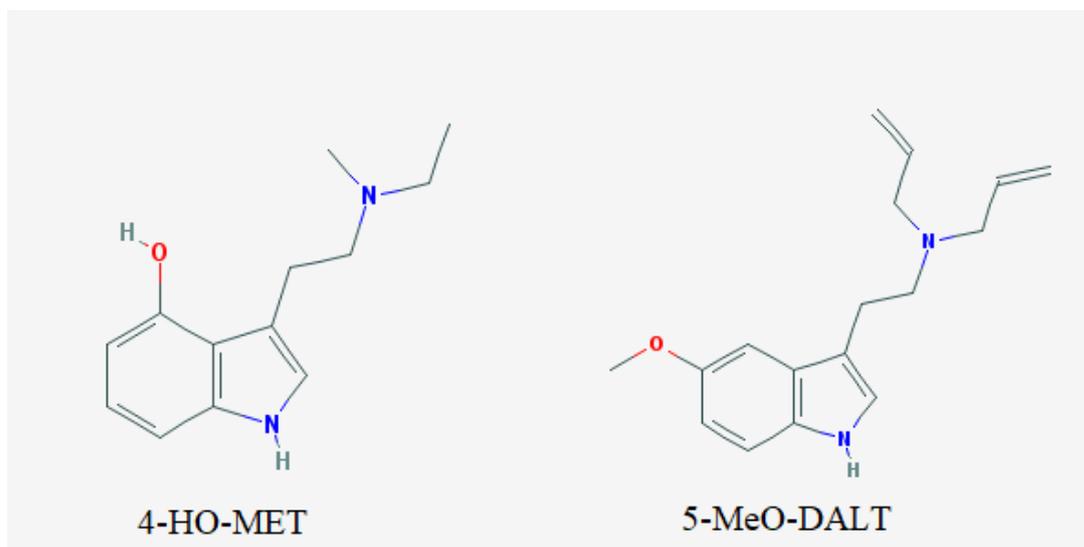


Figure 2. 4-HO-MET and 5-MeO-DALT structure [11].

4-hydroxy-N-methyl-N-ethyltryptamine

4-HO-MET was one of many legal new designer drugs sold on the Internet. Synthesized for the first time by Shulgin in the USA. Oral dosage is 10-20mg, the time of action is 4-6hours. It is white or grey powder and has bitter and sour taste. It is similar to 4-HO-DMT which is naturally present in hallucinogenic fungi.

According to users, the action starts with tingling, followed by decreasing ability to move. Then anxiety, psychic activation and nervousness occur. At the beginning the acuity of vision, contrast and shades of colours in visual perception change, then objects move sinuously and vibrate beyond the contour.

Simple visual patterns occur with open and closed eyes, the patterns change to more complex forms similar to fractales. Sounds are distorted and emerge from nothing.

Synaesthesia in which two senses are mixed occur, e.g. sounds are seen. Users felt overwhelmed with information, had problems with concentration and were—constantly distracted.

Daily activities seemed to be harder to do than usually. Thoughts and feelings were stronger. The ability to discover new perspectives and creative thinking free from patterns and concepts were increased. Such an effect is considered a potential therapeutic success source in the psychedelic therapy. Users experienced euphoria, ecstasy and felt more energetic.

The feelings became negative on certain intensity level. Users felt discomfort, chaos and loss of control. They tried to control the overwhelming intensity of stimuli and distance themselves. Users experienced anxiety, fear and paranoia, as well as somatic symptoms like sweating, chills, tachycardia, headaches, tiredness and insomnia. After whole experiment retrospective reflections, usually positive despite side effects, occurred [17].

5-methoxy-N,N-diallyltryptamine

It is endogenous to humans and is present in the pineal gland and retina. 5-MeO-DALT was synthesized by Shulgin as well. It was initially sold as a “plant fertilizer” or a “plant

food” and confiscated in Helsinki, Finland in 2006 for the first time. 5-MeO-DALT seems to support the protein G activation via 5-HT₁ serotonin receptor.

However, it doesn't affect dopamine, serotonin and noradrenaline reuptake and also represent slight monoamines release activity. It was shown that 5-MeO-DALT is a competitive serotonin reuptake transporter (SERT) inhibitor.

It is mainly powder used orally or intranasally. Average dose fluctuates around 12 to 25 mg, the action begins in 15 minutes, the peak in 30 minutes. The effects last 2-4 hours and include euphoria, difficulties in walking, visual hallucinations and “out of body” experience. The reported side effects include increased neck muscles tension, bruxism, sudden pain in chest, headache and sweating [13]. 5-substituted with methoxy group tryptamines may cause death. The death of a person due to heart failure with polyarteritis nodosa was recorded, it was due to 5-MeO-DiPT overdose. However, no toxic or lethal concentrations of 5-MeO-DALT have been established [18].

Potential therapeutic uses

There is a therapeutic potential for tryptamines. An evidence from 50s and 60s and current studies show that psilocybin can be used to treat alcohol or tobacco addiction and treat anxiety in terminal illnesses. Whereas ayahuasca may be used to treat depression and anxiety, and alcohol or tobacco addiction as the aforementioned [19].

Grob et al. administered psilocybin to people with cancer and found a significant reduction in anxiety and reduction of depression [20].

Other pilot studies on psilocybin found that 9 people who were resistant to obsessive compulsive disorder treatment experienced significant improvement in their symptoms [21]. In addition, pilot studies using ayahuasca in drug addicts show an improvement in psychological well-being and a reduced problem of drug use. As shown by studies of tryptamine, in addition to recreational use, they also have therapeutic potential that can bring significant benefits [6].

3. 3. Lysergamides

Lysergamides are lysergic acid amides belonging to the ergoline group of chemical compounds whose structural skeleton is the alkaloid ergoline [22]. These include lysergic acid diethylamide (LSD) and its analogues. The molecule of LSD consists of an indole system with a tetracyclic ring (C₂₀H₂₅ON₃) (see Figure 3). Carbons 5 and 8 are asymmetric: therefore, four isomeric, optically-active LSD isomers are known, but only the d-LSD isomer has psychedelic effect [23].

LSD-25, commonly known as "acid", is the most popular hallucinogen. It was first received on November 16, 1938 by Albert Hoffman, a Swiss chemist working at the Sandoz plant. In 1943, Hoffman accidentally discovered the psychoactive action of LSD. From this moment LSD played a significant role in the discovery of the serotonin neurotransmitter system.

The pharmacology of lysergic acid diethylamide is complex, but it is known that it acts primarily by binding to serotonin receptors in the brain, especially in the region of the cortex and in the limbic system, which affects the thought processes and auditory and visual perception as other serotonergic psychedelics [24]. Due to the structural similarity with LSD-25 it is considered that other lysergamides act as a partial agonist at the 5-HT_{2A} serotonin

receptor producing the psychedelic experience. Recent research in humans provided evidence for the role of 5-HT_{2A} receptors in the altered state of consciousness: ketanserin (a 5-HT_{2A} receptor antagonist) completely blocked the subjective effects of LSD [25]. It also displays binding activity of dopamine receptors induced in the mechanisms of pleasure and reward what explains the feeling of euphoria. LSD's agonism of D₂ dopamine receptor has been shown to contribute to its psychoactive effects [26]. However, the precise role of these interactions require further investigation.

This compound is physiologically well tolerated and mental reactions can be controlled in a medically supervised settings [27]. Symptoms appear within the first hour of oral intake, reach peak in the second-fourth hour, then gradually disappear. The minimal recognizable dose of LSD in humans is about 25 µg p.o. and significantly changing the state of consciousness is about 75-150 µg p.o. [28].

Due to its hallucinogenic nature, LSD's activity may vary depending on many factors, such as past experience, mood, personality and the environment at the time of use, as well as the dose strength [29]. The duration of lysergic acid diethylamide is colloquially called a trip. Sensory effects, like enhancement of sensory perception or more often its disturbances appear. Visual effects include colored patterns behind closed eyelids, illusion of movement of static surfaces, the appearance of colored geometric patterns moving as well as an intensification of colors and brightness, new textures on objects [30].

Some sensory effects may include disturbances of the sense of time, distorted perception of the body, audiovisual synesthesia, auditory distortions, as well as affective disorders and depersonalization phenomena.

Another psychoactive effect of using LSD is the sense of undergoing a profound mystical or religious experience (unification with the entire universe, direct feeling of the presence of the deity) [31].

Due to the psychoactive nature of lysergic acid diethylamide, there may occur a phenomenon called bad trip, often associated with a negative emotional state, including irrational fears and anxiety, panic attacks, paranoia or involuntary thought of hopelessness.

The adverse effect is a "flashback," which is the intermittent reemergence of perceptual distortions weeks, months or longer after the drug's effects have worn off [6].

The physical effects of the use of lysergamides are: lack of coordination, change in the feeling of heaviness, arrhythmia, hypotension, hyperthermia, increased sweating, dizziness, dry mouth, weakness, mydriasis, hyperglycemia, nausea, vomiting [23]. It leads to uterine contractions, which can increase the risk of miscarriage during pregnancy [22].

Empirical studies suggest no evidence of teratogenic effects from the use of LSD. Mutagenic effects in animals (mice, hamster, and rats) were found only with greatly high doses (up to 500 µg/kg s.c.) [23]. A review study suggests that LSD-25 increases the probability of occurrence of acute psychosis in individuals with a positive family history of schizophrenia [32].

In recent years, several new derivatives of classic LSD were created, which were widespread in Europe as NPS and labeled as research chemicals [33]. Analogues of D-lysergic acid diethylamide present in Poland were identified:

1-Propionyl-*d*-lysergic acid diethylamide also known as **1P-LSD**

6-Allyl-6-nor-lysergic acid diethylamide also known as **AL-LAD**

6-Ethyl-6-nor-lysergic acid diethylamide also known as **ETH-LAD**

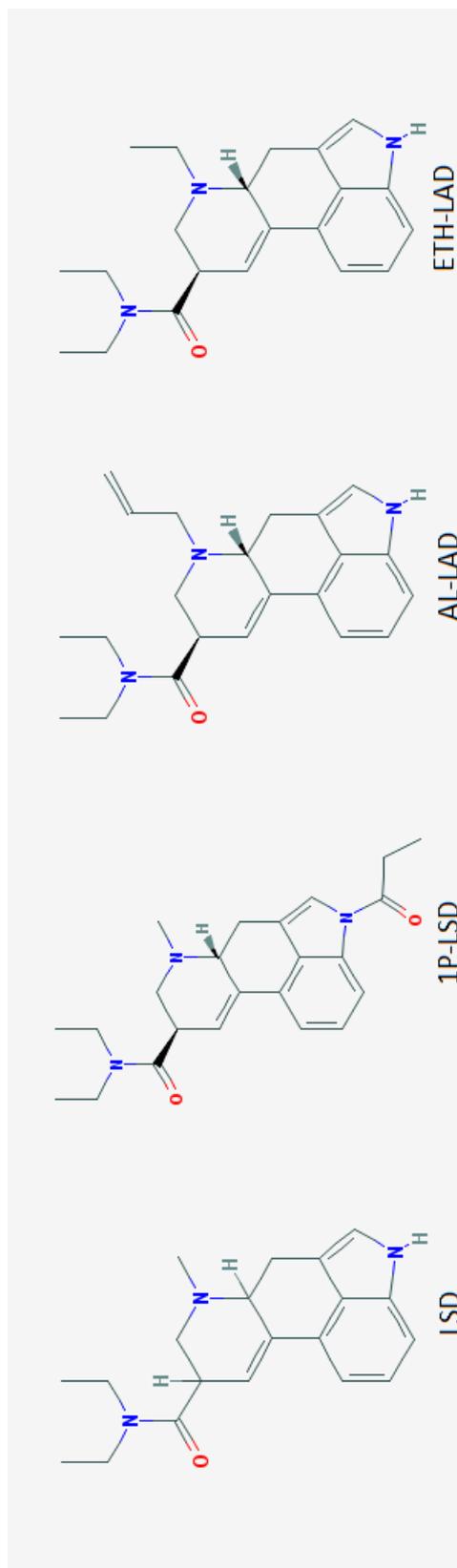


Figure 3. Lysergic acid diethylamide (LSD) and its derivatives that appeared on the new psychoactive substances market [37].

They produce effects resembling those of LSD, having similar pharmacological action at 5-HT_{2A} serotonin receptors, but possessing different potencies, start effects and duration (see Table 1) [34].

Table 1. Duration and common dosage of LSD-25 and its analogues [35].

Name of substance	duration	common dosage (μg)
LSD-25	6-12h	75-150
AL-LAD	6-10h	80-160
ETH-LAD	8-12h	40-150
1P-LSD	8-12h	75-150

Users noticed that the strength of effect, urge to use more drugs and risk of harm following use were significantly lower for LSD analogues compared with LSD-25 [35].

The most popular form of lysergic acid diethylamide analogues is a liquid transferred onto a small paper square (known as "blotter"). All of these compounds are most often sold in the form of blotters containing 100 or 150 micrograms of the substance. Users usually put it under the tongue. Onset of action is not immediate, taking from 20 minutes to 1 hour before any effect is noted.

LSD-25 does not lead to addiction and there have been no documented human deaths from LSD overdose, however toxicity and long-term health effects of recreational use of the LSD analogues do not appear to be studied in any scientific context and the exact toxic dose is unknown [36]. Due to the fact that they are NPS with a very limited history of human exploitation.

There is very limited scientific data about their pharmacological properties, but they have been well received by the community since they appeared on the NPS market.

1-Propionyl-d-lysergic acid diethylamide

1P-LSD is named for the propionyl group bound to the nitrogen of the polycyclic indole group of LSD.

Polish law prohibits the sale of LSD. In connection with these limitations, 1-propionyl-LSD, also known as 1P-LSD, became available as a "research chemical" together with AL-LAD and ETH-LAD.

The original synthesis date of 1P-LSD is not known. The first user reports of polish drug forums appeared in January 2015. There is very little data on the pharmacologic properties, metabolism and toxicity of 1-Propionyl-d-lysergic acid diethylamide. It is assumed that it has a similar toxicity and risk profile as lysergic acid diethylamide.

It is noticed that its action is weaker than the parent LSD-25. Brandt et al. conducted a research study on male mice and proved that 1P-LSD shows only 28% the potency of LSD [38].

N1-substituted lysergamides undergo N1-dealkylation in vivo [39]. Due to this fact it was proven that 1P-LSD hydrolyze to LSD when exposed to human serum what indicated that it served as a pro-drug for LSD-25 although it does not appear to have been empirically confirmed [38].

The effects of using 1-Propionyl-d-lysergic are not well defined. It is thought to be comparable to that of lysergic acid diethylamide [40]. Forum users' reports indicate that the subjective symptoms of taking 1P-LSD are very similar to the parent LSD. 1-Propionyl-d-lysergic acid diethylamide, however, has a more confusing effect and gives a better listening experience than the other lysergamides NPS.

6-Allyl-6-nor-lysergic acid diethylamide

AL-LAD was first studied in 1984 by Andrew J. Hoffman as an LSD analogue however it only entered the research chemical market in the 2013s [41].

Instead of a methyl group at the position, like LSD has, AL-LAD is substituted at R6 with an allyl group comprised of a methylene bridge bound to a vinyl substituent. Which is similar to the substitutions found on ETH-LAD than 1P-LSD (see Figure 3).

Receptor binding studies showed that AL-LAD displays high affinity for 5-HT_{2A} receptors in rat frontal cortex homogenates [42]. In contrast 6-Allyl-6-nor-lysergic acid diethylamide showed a lower affinity for D1 and D2 dopaminergic receptors than for LSD [43].

Activation of 5-HT_{2A} serotonin receptors is manifested by a rapid side-to-side rotational head movement (HTR), which is used to assess hallucinogenic effects in rodents [44]. This method was used in the research conducted by Brandt et al. who have shown that AL-LAD demonstrated similar to LSD head-twitch response (HTR) in male mice [42].

A number of anecdotal human reports have been presented by Alexander Shulgin and described as less strong and less dramatic than LSD-25. It is often described as being more visually-oriented than others lysergamides but simultaneously has shorter duration of action (6-8h) than LSD and less negative physical side effects as produce anxiety, panic or confusion.

6-Ethyl-6-nor-lysergic acid diethylamide

ETH-LAD was introduced to the research chemical market in the 2016s.

In contrast to LSD-25, 6-Ethyl-6-nor-lysergic acid diethylamide does not contain a methyl group substituted at 6 position of its nor-lysergic acid skeleton but substituted with an ethyl group.

ETH-LAD is not a prodrug of LSD-25 because this would require dealkylation followed by re-methylation, which would be a rather improbable degradation route.

Similar to LSD, ETH-LAD has high affinity for 5-HT_{2A} receptors, dopamine D1 receptors and dopamine D2 receptors [43].

The use of this compound by humans was documented for the first time in 1997 by Shulgin (in his book titled: TIHKAL. The Continuation), who state that 6-Ethyl-6-nor-lysergic acid diethylamide produce hallucinogenic effects in humans at lower doses than LSD-25. ETH-LAD is regarded as more visually and auditorily distortive, introspective, analytical and immersive. Further it causes excessive physical effects such as severe nausea or bodily discomfort.

Moreover, animal studies also confirmed that 6-Ethyl-6-nor-lysergic acid diethylamide is significantly more potent than LSD [41].

LSD: a new treatment emerging for the past

Studies on the usefulness of LSD in the therapeutic context have been resumed after a long suspension.

LSD-assisted psychotherapy was primarily explored for treating alcoholism. Meta-analysis of 6 studies involving 536 patients showed a connection between a single dose of LSD and a reduction in alcohol consumption by alcoholics in conjunction with various alcoholism treatment programs [45].

In 2014 it was proved that LSD is useful in reducing pain, improving mood and decreasing fear of death in patients suffering from anxiety and other problems associated with terminal illness. Participants reported reduced anxiety (77.8%) and increased quality of life (66.7%) since their study participation [27].

An interview conducted among people suffering from a cluster headache showed that LSD-25 is capable of reducing pain and extending the periods between successive attacks [46]. Other recent pilot studies found that LSD may increase creative imagination and suggestibility in healthy volunteers [47]. Studies have shown that suggestion is a central factor in treating depression [48]. Therefore, LSD may be used to treat depression.

Therefore, It can be assumed, that the Lysergic acid diethylamide analogues mentioned in this article, due to their similar chemical structure and effect may also be a legal alternative used for treatment in the future.

3. CONCLUSIONS

It should be noted that these information were collected during a period when some tryptamines and LSD analogues were still legal in Poland, therefore this trend may be subject to change in the following year. New compounds are emerging based on the structure of compounds already known and often previously banned. New laws and restrictions are being introduced to prevent the distribution and use of new psychoactive substances in Poland. The profile of LSD analogues was reported to be very similar to LSD. The effects of intake of various tryptamines are almost the same. In connection with the fact that NPS described in this paper are relatively new, they should be examined to establish their level of toxicity and pharmacology as they may be of interest as potential therapeutics.

Psychedelics represent a smaller percentage of NPS, but they are still an important problem in the struggle with designer drugs. However, they have profound effects on human consciousness and exhibit a collection of remarkable properties which, when applied skillfully, can promote healing or wellbeing.

It may not be completely surprising if the next generation of antidepressants, psychotherapy counselling aid were to come from psychodysleptic NPS. Further research is needed to explain the psychopharmacological effects of these substances. Chemical and pharmacological data obtained from NPS can help research environments that are interested in various aspects related to the use of substances.

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Additional Quoting

Dziennik Ustaw z 2005 r. Nr 179 poz. 1485 Ustawa z dnia 29 lipca 2005 r. o przeciwdziałaniu narkomanii (The Act of 29 July 2005 on counteracting drug addiction JL 2005 No.179 item. 1485). (Poland)

Dziennik Ustaw z 2010 r. Nr 213 poz. 1396 Ustawa z dnia 8 października 2010 r. o zmianie ustawy o przeciwdziałaniu narkomanii i ustawy o Państwowej Inspekcji Sanitarnej (Act of 8 October 2010 amending the Act on counteracting drug addiction and State Sanitary Inspection, JL 2010, No. 213, item. 1396). (Poland)

Dziennik Ustaw z 2009 r. Nr 63 poz. 520 Ustawa z dnia 20 marca 2009 r. o zmianie ustawy o przeciwdziałaniu narkomanii (Act of 20 March 2009 amending the Act on counteracting drug addiction, JL 2009, No. 63, item. 520). (Poland)

Dziennik Ustaw z 2010 r. Nr 143 poz. 962 Ustawa z dnia 10 czerwca 2010 r. o zmianie ustawy o przeciwdziałaniu narkomanii (Act of 10 June 2010 amending the Act on counteracting drug addiction, JL 2009, No. 143, item. 962). (Poland)

Dziennik Ustaw z 2011 r. Nr 105 poz. 614 Ustawa z dnia 15 kwietnia 2011 r. o zmianie ustawy o przeciwdziałaniu narkomanii (Act of 15 April 2011 amending the Act on counteracting drug addiction, JL 2011, No. 105, item. 614). (Poland)

Dziennik Ustaw z 2015 r. poz. 875 Ustawa z dnia 24 kwietnia 2015 r. o zmianie ustawy o przeciwdziałaniu narkomanii oraz niektórych innych ustaw. (Act of 24 April 2015 amending the Act on counteracting drug addiction and some other acts. JL 2015, item. 875). (Poland)

Dziennik Ustaw z 2018 r. poz. 1490 Ustawa z dnia 20 lipca 2018 r. o zmianie ustawy o przeciwdziałaniu narkomanii oraz ustawy o Państwowej Inspekcji Sanitarnej. (Act of 20 July 2018 amending the Act on counteracting drug addiction and State Sanitary Inspection, JL 2018, item. 1490). (Poland)