LSD/psylocybin/DMT in Depression Treatment

Subjects: Psychology, Applied

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Despite many different kinds of substances available for depression treatment, depression itself still appears to be a clinical challenge. Recently, formerly illicit substances came to scientists' attention, including lysergic acid diethylamide (LSD), psilocybin and dimethyltryptamine (DMT). Some studies suggest that these substances might be effective in depression treatment.

Keywords: lysergic acid diethylamide (LSD) ; psilocybin ; dimethyltryptamine (DMT) ; depression

1. Introduction

Lysergic acid diethylamide (LSD) is a semisynthetic substance derived from the lysergic acid of the fungus *Caliceps purpurea*. LSD is mainly taken orally, but it can also be smoked, snorted or injected [1]. This substance exists in the form of four isomers, of which only the d-LSD form has psychoactive properties [2]. LSD has been shown to be an agonist of 5HT2a, 5HT1a and 5HT2c receptors. By affecting the 5HT2a receptor (and indirectly by enhancing glutamatergic transmission in the prefrontal cortex and alterations in cortico-cortical and cortico-subcortical transmission), LSD use results in a hallucinogenic effect [3]. The effects of LSD use are also associated with its pleiotropic effects because, in addition to its affinity for serotonin receptors, LSD also affects dopamine receptors (D1, D2, D4) and indirectly affects glutamatergic neurotransmission and TAAR receptors (in animal models). LSD also affects alpha-2 adrenergic receptors to a small extent, stimulating the sympathetic nervous system, resulting in an increase in body temperature, sweating, tachycardia, increased blood pressure and muscle tension, which are the first to occur after LSD ingestion [4]. Doses greater than 100 ug cause heightened sensory perceptions, synesthesias, pseudohallucinations, changes in time perception, feelings of depersonalization and derealization [5]. Unlike other psychoactive substances, no physical dependence has been observed, and low toxicity has been noted [6].

Psilocybin is one of the major psychedelic agents found in certain species of mushrooms around the world. Psilocybin is an agonist of 5HT2a serotonin receptors; however, unlike LSD, it has no effect on dopamine receptors [7]. The undisputed advantage of this tryptamine derivative is its low toxicity, minimal side effects and lack of substance dependence [8]. The effects of psilocybin depend on the dose administered—at an amount of about 20 mg taken at one time, users experience a state of altered consciousness, increased introspection and hypnagogic experiences. Perceptual changes such as synesthesia, delusions and alterations in the sense of time are also observed. The effects of the hallucinogen are mainly associated with the activation of 5HT2a receptors in the thalamus, reducing the activity of these areas [7][9]. In animal models, vegetative changes such as mydriasis, tachycardia, a slight increase in blood pressure and hyperglycemia have also been observed after ingestion of this substance. The main metabolite of psilocybin, produced by hepatic metabolism, is psilocin, and the mean elimination time of it is about 50 min [9].

DMT, or dimethyltryptamine, is a psychedelic substance commonly found in plants and in the organisms of some mammals, including humans. DMT is produced endogenously in the pineal gland in small amounts, and its role is not yet known [10]. DMT is an agonist of 5-HT1A, 5-HT1B, 5-HT1D, 5-HT1E, 5-HT2A, 5-HT2B and 5-HT2C receptors and a partial agonist of 5-HT5A, 5-HT6 and 5-HT7. The hallucinogenic effect is mainly achieved by stimulating the 5-HT2A receptor and enhancing presynaptic glutamatergic transmission in the prefrontal cortex [11]. DMT can be ingested, inhaled, injected intravenously or inflamed. In the first case, it must be taken together with monoamine oxidase A inhibitors since DMT is metabolized in the first pass through the liver with the help of this enzyme [12]. Depending on the route of ingestion, DMT causes psychedelic effects of varying severity (from mild agitation to visual and auditory hallucinations) depending on the metabolite content in plasma, but the subjective effects remain similar to those associated with the use of LSD and psilocybin, which is associated with similar effects of these substances via the 5-HT2A receptor to the central nervous system [13][14]. The most common side effects of DMT use are vomiting and diarrhea [11]. It is estimated that ingestion of DMT at doses used to achieve psychedelic effects (i.e., up to 100 mg) is not toxic to mammals, and dependence is very

rare [12]. Renal metabolism dominates, the main metabolites detected in urine are 3-indoleacetic acid and 3-indoacetic acid, and the half-life in the body ranges from a few minutes to several hours depending on the route of administration [12].

2. Lysergic Acid Diethylamide, Psilocybin and Dimethyltryptamine in Depression Treatment

Recently, ketamine has emerged as a new therapeutic option for drug-resistant depression, which until recently was associated by psychiatrists primarily as an anesthetic or as a component of the patient's polytoxicomania. At the same time, research is being conducted into the use of another substance that is illegal in most countries, 3,4-methylenedioxymethamphetamine (MDMA), popularly known as ecstasy, in the treatment of drug-resistant post-traumatic stress disorder (PTSD). Research is well advanced, and it is possible that MDMA will be approved as a drug by the FDA by 2022 [15]. For these reasons, scientists worldwide are exploring other, previously known as illicit, drug substances. According to the Global Drug Survey 2020 report by an independent UK scientific organization that studies the impact of psychoactive substance use on mental health, 8 of the 20 most commonly used psychoactive substances in 2020 are in the psychedelics and dissociatives group: in the past 12 months, 21.0% of respondents have used LSD, psilocybin mushrooms were used by 16.1% of respondents and DMT by 4.8% of respondents. These data come from over 110,000 individuals from over 25 countries, mostly in Europe [16]. By comparison, the 2019 Global Drug Survey reports that in the past 12 months, 17.5% of respondents have used LSD, 14.8% of respondents have used psilocybin mushrooms, and 4.2% of respondents have used DMT [17]. Equally popular is the interest in treating depression with psychedelics. On 23 June 2021, the Google search engine returned 2,310,000 results for the query "psychedelic treatment for depression", and the topic is covered by well-known media outlets such as the BBC and Daily Mail [18][19]. Due to the increasing popularity of psychedelics in society, it is important to conduct further multidirectional research on them, including not only their use in therapy but also broadly understood public health issues, which is why the authors decided to conduct a systematic review of these substances in depression treatment.

We did not find any studies on LSD use in depression treatment even though the three substances share very similar mechanisms of action, which justifies conducting such studies.

Six studies were included in the analysis. The total number of participants included in the psilocybin studies ranged from 12 to 51, both male and female. Subjects were adults. In three studies the sample was composed of subjects with major depressive disorder [20][21][22], and in the other three studies the sample was composed of subjects with depression and anxiety in the course of life-threatening cancer [23][24][25]. Three out of six of the psilocybin studies were rated strong. Psilocybin is the best documented substance in depression treatment from the three substances, which makes psilocybin in a medical setting a very promising treatment option for patients with depression.

Only one out of four DMT studies was rated high. Three out of four of the DMT studies included were non-RCT studies, which do not allow to draw final conclusions on efficiency in depression treatment. No clinical studies of DMT use alone in depression treatment were found, as all of the included studies dosed ayahuasca, and it should be remembered that ayahuasca is administered with monoamine oxidase inhibitors, which may have an effect on mood themselves. It should also be remembered that ayahuasca contains other alkaloids, such as harmine or harmaline, and since it is a decoction of the plants themselves, it is difficult to estimate the dose of alkaloids consumed [26][27].

The use of psychedelic substances is not without risks. The pharmacology and mechanism of action of each substance is fairly well understood, and while LSD, psilocybin and DMT have relatively low health and life risks somatically, the risk of psychiatric complications must be considered. In addition to psychosis, another clinically significant complication that can occur after even a single ingestion of a psychedelic substance is Hallucinogen Persisting Perception Disorder or HPPD for short, classified as F16 in ICD-10 and 292.89 in DSM-V. This disorder manifests as chronic perceptual changes that can interfere with daily functioning and reduce quality of life and satisfaction. Duration is an individual matter, usually transient symptoms lasting from a few minutes to several months, although in extreme cases symptoms can last throughout life [28]. There are two types of HPPD: type 1, in which there is a brief recurrence of psychedelic effects in the form of a "flashback", occurs in 1:20 people, and type 2, which occurs less frequently, in 1:50,000 and in which symptoms are chronic. Since the etiology and scientifically proven treatments remain unknown, HPPD should be considered a significant risk for patients undergoing treatment with psychedelics [29].

3. Conclusions

Psilocybin and DMT could be efficient and useful in depression treatment, but further studies and observations on bigger groups of patients are still required to assess safety. Considering social interest in psychedelics, studies for LSD use in depression treatment are urgent.

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