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By Larissa Conti Herrero, Esther Soneghet Baiocco e Silva, Vitória Patrícia Rodrigues Cunha, Layanne Bosse, Mariana Isabella de Medina Satriano, Roberta Wassita Curi Schumann Rosso, Ana Beatriz Sales Vieira, Maria Jeane Veras Resende, Julia Pessoa de Melo Seixas, Lucas Belém Pessôa de Melo Guerra Seixas, Clarice de Abreu Pereira, Gabriella Martucci Manca, Carolina Santoro Bueno, Paula Teixeira Silva, Marina Costa Florio, Juliane Alves de Mesquita, Raphael Vinicius Mendes Abreu, Édimo Júnior Queiroz Oliveira, Andressa Akiko Koshikumo, Fernanda Garzedim Santos de Abreu & Dra. Aline de Amorim Duarte

Summary- Introduction: When analyzing the main depressive conditions and their treatments, we understand that it is not so simple to take care of psychosomatic conditions, because it is a pathology that has a significant epidemiological aspect and needs a good approach, therefore, psychedelic drugs come in as an important alternative as a treatment.

Methodology: This is a literature review with research in databases, using 60 scientific articles as a basis and being filtered based on scientific impact and approach.

Results: Psychedelic agents are chemical substances that, in non-toxic doses, produce changes in conception and thinking in a state of mind, thus altering perception and reason.

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Psychedelic Drugs used in the Treatment of Depression: A Literature Review

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Summary- Introduction: When analyzing the main depressive conditions and their treatments, we understand that it is not so simple to take care of psychosomatic conditions, because it is a pathology that has a significant epidemiological aspect and needs a good approach, therefore, psychedelic drugs come in as an important alternative as a treatment.

Methodology: This is a literature review with research in databases, using 60 scientific articles as a basis and being filtered based on scientific impact and approach.

Results: Psychedelic agents are chemical substances that, in non-toxic doses, produce changes in conception and thinking in a state of mind, thus altering perception and reason. There are several substances with psychedelic actions, many of which are banned and considered illegal in several countries around the world, however there are regulators that regulate various drugs and substances, and many of these deserve attention, due to the great evolution in the scientific technical environment.

Final considerations: It is important to understand the mechanism and how to analyze depressive conditions, as well as adjust changes in life, practices and quality of life.

I. INTRODUCTION

Psychiatric disorders are responsible for affecting more than 350 million people worldwide. Brazil is, according to the World Health Organization (WHO), the country with the highest number of individuals with anxiety disorders, in addition to leading the ranking in Latin America with the incidence rate of depressive disorders.

Depression is characterized as a multifactorial pathology directly affecting quality of life, in addition to generating physical and mental impacts. There are no pathognomonic symptoms of depression, but there are characteristic symptoms, these include insomnia, fatigue, decreased appetite, anhedonia, suicidal thoughts, and weight loss or gain. Depression is the disease that leads third place as a burden of disease worldwide, where the impact of mortality and morbidity of various pathologies is measured, and according to the World Health Organization, by 2030, depression will be in first place. Thus, for the diagnosis of depression

and treatment, it is important to rule out other psychiatric disorders such as anxiety or bipolar disorder. The treatment for this disease is still widely studied, several classes of drugs demonstrate success in certain cases and therapeutic failure in others, thus showing the need for different therapeutic means.

Thus, new therapeutic means such as the use of psychedelics such as LSD and MDMA gain strength in the study of treatments for depression and other psychiatric disorders such as Generalized Anxiety Disorder. However, the repeated use of psychedelics can lead to the development of tolerance due to the decrease in specific receptors of these substances in neurons, and therefore it must be well indicated and monitored by specialists, with the aim of achieving beneficial therapeutic responses for the patient.

II. METHODOLOGY

This is a literature review, whose bases were taken from the SciELO and PubMed data platforms. The research period was from July 2023, meeting the inclusion criteria which were articles from the years 2000 to 2023, in Portuguese and English, online texts and in full texts. As strategies for better evaluation of the texts, the following health descriptors (DeCS) were used: "Psychedelic drugs", "Depression" and "Mental health".

III. RESULTS AND DISCUSSION

Psychedelic agents are chemical substances that, in non-toxic doses, produce changes in thinking and thinking in a mood, thereby altering perception and reason. (VACCARINO, et al., 2006) (GOMES; MUNIZ; PAULINO, 2016; JOHNSON, RICHARDS, GRIFFTHS, 2008). There are several substances with psychedelic actions, many of which are banned and considered illegal in several countries around the world, however there are regulators that regulate various drugs and substances, and many of these deserve attention, due to the great evolution in the scientific technical environment (ESCOBAR et al. al., 2010). Psychedelics

can be found naturally in fungi, animals and plants or be synthesized (CARHART-HARRIS et al., 2017).

Psychedelics are, for the most part, substances with action capable of altering perception and consciousness in a marked and innovative way (CARHART-HARRIS et al., 2017). Based on the pharmacological profile, substances can be divided as follows: classical psychedelics (serotonin 2A [5HT-2A] receptor agonists), empathogens or entactogenics (mixed serotonin and dopamine reuptake inhibitors and releasers) dissociative anesthetic agents (serotonin and dopamine reuptake antagonists) N-methyl-D-aspartate [NMDA]) and atypical hallucinogens, which affect multiple neurotransmitter systems (GARCIA-ROMEU; KERSSGAARD; ADDY, 2016).

Classic psychedelics, the class that will be discussed in this study, interact with serotonin receptors, these receptors mediate emotions and moods such as anxiety, learning memory, cognition, appetite and other biological processes. They are substances with agonist action on serotonergic 2A receptors capable of changing perception and consciousness in a marked and innovative way (CARHART-HARRIS et al., 2017). These receptors are located in the central and peripheral nervous system and thus can be used to treat diseases such as anxiety and depression (LOWE et al., 2021).

The class of psychedelic substances has a relatively high score in psychological and physiological safety if used under supervision in a monitored environment, they generally do not induce dependence or adverse effects that cannot be controlled in adequate doses and in the presence of someone who is able to offer psychological support, if necessary (KUYPERS, 2020).

The treatment performed with hallucinogens brings acute effects that are divided into two dimensions. The first is the physiological dimension which is described as the direct effect of the intervention on the brain. The second is the psychological dimension, which is described as the subjective experience reported by the individual. These acute brain effects include both direct and secondary effects. The direct effects are mediated through the serotonin receptor, while the secondary effects are mediated through the glutamate receptors (COUTO, 2017).

The use of psychedelics in mental health, and in medicine as a whole, has been portrayed in the literature for decades. Since the first trials with Lysergic Acid Diethylamine (LSD), in 1950, psychedelics had a brief contact with psychology and psychiatry, until their prohibition in the mid-60s. of mood disorders, smoking and alcoholism, prior to its ban (CARHART-HARRIS & GOODWIN, 2017). There are several substances with psychedelic actions, many of which are banned and considered illegal in several countries around the world, however there are regulators that regulate various drugs

and substances, and many of these deserve attention, due to the great evolution in the scientific technical environment (ESCOBAR et al. al., 2010).

In Brazil, the presence of psychedelics, especially in clinical trials, occurs mainly through LSD and MDMA - synthetic substances - in addition to psilocybin, ayahuasca and ibogaine, which have their origin in nature (BRAZILIANS STUDY PSYCHEDELIC DRUGS TO TREAT DEPRESSION AND CHEMICAL DEPENDENCE - BBC, 2020). Substances of prohibited use in Brazil, according to ANVISA (2017), are substances considered prohibited, which means that despite the growing research on the use of psilocybin for pharmacological purposes, at least in Brazil there are still no cases of synthesized use mediated by law, and much less production of medicines with this substance.

There are different types of depressive disorders, with psychotic features or not, and they can be catatonic, chronic, seasonal or atypical. The depressive picture as a whole, which is characterized by: sleep disturbances, such as insomnia or hypersomnolence; several awakenings during the night, causing a poor use of sleep; changes in appetite, which may include loss of appetite or excess appetite; children may not have the expected weight for the corresponding age; increased appetite is heightened by carbohydrates and sweets; decreased libido; social withdrawal; excessive crying; suicidal thoughts or behaviors; psychomotor retardation and generalized slowing, or psychomotor agitation; patients often report a feeling of heaviness in the limbs (PORTO, 1999)(IBANEZ et al., 2014).

Drug treatment constitutes the foundation of therapeutic intervention to reduce the duration and intensity of the symptoms of the current episode and, above all, to prevent its recurrence. Since adherence to treatment is one of the main causes of relapse (LAFER et al., 2000). However, the advancement of pharmacology aimed at the central nervous system in recent years has seen a remarkable development, but the use of classic drugs to treat depression remains in some patients without effect or experience withdrawal effects or adverse effects, being essential to search for new approaches to treatment of depression (GOLDBERG et al., 2020) (PAHO, 2018) (GILL et al., 2020).

Classic psychedelics, such as LSD, DMT and more specifically psilocybin, have proven to be highly efficient in the treatment of refractory depression, with improvement in symptoms, good tolerability and good adherence, since there is no need for hospitalization during treatment. Studies have shown a decrease in amygdala reactivity with psilocybin, in addition to an increase in the positive mood state, a region that becomes hyperactivated in depressive patients.

An average dose of lysergic acid diethylamide will significantly alter the user's state of consciousness,

or psilocybin (commonly known as "LSD"). Such a change will be characterized by euphoria, increased capacity for introspection, visual hallucinations, synesthesia (mixtures of senses, where the experimenter can "hear a color" or "see a sound"), acceleration of thought and changes in the perception of space and time. . Changes in body image and ego function may also occur (PASSIE et al., 2008; CARHART-HARRIS et al., 2016). According to Lee et al. (2012) psilocybin has the mechanism of action to decrease brain activity and connectivity. This substance, which is inactive, is metabolized to the active ingredient psilocin, which in turn activates many neurotransmitter receptors to modulate activity in excitatory and inhibitory GABA-ergic neurons. In clinical trials, there was a marked reduction in depressive symptoms in volunteers affected by major depressive disorder (MDD) resistant to antidepressant therapy in the first 5 weeks post-treatment. In this study, in which only 2 doses of psilocybin were used, 65% of patients met the parameters for remission, remaining so 3 and 6 months after administration (CARHART-HARRIS ET AL., 2018)

In another study carried out by Ibanez et al. (2014) with patients undergoing treatment for depression with prescribed pharmacology, one of the problems observed was the weariness of the patient caused by the drug treatment, which, although necessary to reduce depressive symptoms, did not always provide results that matched the expectations of patients. In addition, low adherence to pharmacotherapy and lack of knowledge regarding the therapy used by patients were also observed, factors that made treatment difficult.

Another drug being studied for the treatment of depressive disorder is methylenedioxy-methamphetamine (MDMA, popularly known as "Ecstasy"), a synthetic compound capable of producing a state of excitement and disinhibition, enhancing physical sensations, empathy and interpersonal proximity, not causing hallucinatory visions, like other psychedelics. In the brain, it stimulates neurons to release more neurotransmitters such as serotonin, noradrenaline and dopamine throughout the central nervous system, accelerating reasoning and intensifying emotions. Thus, changes in mood and perception are attributed to the release of dopamine and serotonin, while changes in body temperature occur through the action of all (dopamine, serotonin and noradrenaline). In addition, MDMA acts as an indirect agonist at the presynaptic serotonergic receptor, which not only increases serotonin release but also inhibits its reuptake. It also acts as an inhibitor of the enzyme monoamine oxidase (MAO), increasing the concentration and release of serotonin in the central nervous system. The action of the substance begins with 30 to 60 minutes of its use and lasts for up to 6 hours. This drug has also been shown to be quite

efficient in the treatment of Generalized Anxiety Disorder (GAD). (SAIBER, 2021)

Another psychedelic under study is Ayahuasca, a tea produced with various plants originating in the Amazon and historically used in indigenous rituals. It is a drug that has in its composition dimethyltryptamine, a psychoactive, being able to increase neuroplasticity, facilitate adaptive neural architectural changes and break pathological associations, triggers and cues associated with addiction. How psychedelic images are represented in the brain and what are the neural bases of introspection and self-analysis of emotions, a process reported by users during the effect of the substance. Studies in Brazilian universities have shown positive effects of the substance in treatments for chronic depression and chemical dependency, and it is possible to observe improvement with the administration of a single session (TALIN, P; SANABRIA, E, 2017).

The drug has an anti-inflammatory effect, thus decreasing the pro-inflammatory state that patients with depressive disorder may have, increasing the effectiveness of the immune system response. People with depression often have a change in a protein called "brain-derived neurotrophic factor" (BDNF). This chemical marker is connected to neuroplasticity, that is, the ability of the neural system to promote new synapses, which also undergoes modifications with the use of the drug.

Psychedelic drugs have been researched for different treatments, such as anxiety in terminal patients, obsessive-compulsive disorder, headache, addictions and resistant depression, in addition to the debate that it raises about mystical experiences and their management in the clinic. In addition, positive effects of psilocybin were observed, which are atypical results for a pharmacotherapeutic treatment, whose effects do not last for so long (COUTO, 2017).

Also, it can be observed that, in the evaluation of the use of psychedelics in the treatment of chemical dependencies, there was a favorable result in the study aimed at smoking cessation (JOHNSON, GARCIA-ROMEU & GRIFFITHS, 2016). In addition, psilocybin has also been shown to be effective in maintaining abstinence in alcohol-dependent patients (BOGENSCHUTZ ET AL., 2015).

Repeated administration of psychedelics leads to a rapid development of tolerance known as tachyphylaxis, a phenomenon that may result from decreased expression of 5-HT_{2A} receptors on neuron membranes. For example, the daily administration of LSD essentially leads to the complete loss of sensitivity to the effects of the drug on the fourth day of taking it (CHOLDEN; KURLAND; SAVAGE, 1955).

IV. FINAL CONSIDERATIONS

After the above, it is understood that psychosomatic illnesses have a significant epidemiological character in the population of the 21st century, in view of this, several treatment mechanisms have emerged as an important alternative since conventional treatments arise with various adversities, treatment with psychedelics comes as a strong path of treatment, with new possibilities and with less adverse effects than those presented in normal drugs, being an important way to improve the quality of life, mental health of the entire population, with the correct use and accompanied by a professional of trained health.

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