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Review

Psychedelic Chemicals and Depression Treatment

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ABSTRACT

Depression is a psychiatric disorder that is widespread around the world and affects more than 300 million individuals. Treatment of depression divides into psychological counseling and antidepressant medication. Although antidepressants are an effective method of treating depression, alternative treatments are necessary due to their strong adverse effects. As an alternative treatment of depression, commonly used psychedelics are classic serotonergic psychedelics, entactogens, the atypical psychedelic ibogaine, and dissociative anesthetics. Psilocybin in particular, as well as LSD (lysergic acid diethylamide) and ayahuasca containing DMT (N, N-dimethyltryptamine), are seen as promising novel treatments for depression. In this review, the effect of psychedelic drugs, in particular LSD, psilocybin, and DMT on the treatment of depression will be discussed.

Keywords: Ayahuasca, depression, lysergic acid diethylamide, psilocybin, psychedelics.

DEPRESSION

Depression or major depressive disorder (MDD) is the most common and debilitating psychiatric disorder, with more than 300 million individuals to suffer around the world.[1] Depression differs from the usual mood swings and short-term emotional responses to daily life challenges in terms of depressed mood such as sad, empty, and irritable feelings, lack of interest in formerly activities, loss or increased appetite, loss of energy, sleep disturbances, trouble concentrating, difficulty making a decision, negative thoughts about oneself or others, feelings of worthlessness, hopelessness, and guilt, and at its worst, thoughts of suicide.[2]

The most basic way to diagnose depression is a high degree of clinical suspicion. In general, clinicians take the detailed history that includes specific symptoms that clients expressed their own besides that assessment tools such as Beck Depression Inventory (BDI), Hamilton Depression Rating Scale (HAM-D), or the General Health Questionnaire (GHQ) to assess depression.[3,4]

ETIOLOGY OF DEPRESSION

There is no single reason that explains depression, and sometimes individuals who live in good conditions experience it. Depression usually consists of not just one cause, but a combination of many causes. Both environmental and biological factors can cause depression in people. Many psychological theories and approaches have interpreted causes of depression in different ways. The psychodynamic approach focuses on the inner world conflicts that occur in the client's consciousness.[5] According to cognitive theories of depression, individuals who have maladaptive cognitive beliefs such as negative thoughts about themselves, the world, or others tend to have depression when they encounter a stressful life event.[6] In the humanistic approach, the pyramid of Maslow's "Hierarchy of Needs"[7] that represents ours needs to fulfill in a lifetime period is used as a base to explain the cause of depression. At the top of the pyramid, there is the “self-actualization”

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that final stage individuals have innate drives to develop their potential. If anything prevents to become "self-actualized" that can be a cause of depression.[8]

THE NEUROBIOLOGY OF DEPRESSION

Depression has a set of complex biological processes that include genetics, brain structure and function, neurotransmitter and neuroendocrine, and immune system. The broader picture of the neurobiology of depression is not fully understood, it is known that both environmental and genetics play a very important role in this area.[9]

Twin studies on depression point to a very strong hereditary effect, which shows that separate genetic factors from environmental factors. According to twin studies on individuals with depression showed that about one-third of the risk derived from genetic differences between individuals.[10,11] Those research also provide that genes can explain 50% to 70% of the etiology of depression.[12]

Changes in neuroendocrine and behavioral responses in individuals with depression can be caused initially by an abnormal biogenic amine-containing neuron. Also, dysfunction in the immune system and acceleration of inflammatory reactions may induce depression.[13]

Individuals with depression have higher than normal levels of the stress hormone cortisol, which leads to neuronal damage, particularly, in the hippocampus. The stress-responsive hypothalamic-pituitary-adrenal axis (HPA) with increased cortisol concentrations and dexamethasone non-suppression could induce abnormalities in individuals with depression.[14]

Brain-derived neurotrophic factor (BDNF) plays a crucial role in nerve growth, sustainability, and development that is active in the hippocampus which is important in learning, memory, and thinking. Serum BDNF concentrations are decreased in individuals with depression.[15,16]

Dysfunction in the monoamine neurotransmitters has been associated with the neurobiology of several mood disorders. Two neurotransmitters that play a fundamental role in the emergence of depression are noradrenaline and serotonin (5-HT/5-hydroxytryptamine). An interruption in noradrenaline production and destruction makes the individual vulnerable to any stressful situation.[12] Serotonin was found to be abnormal in many individuals with depression.[17]

Neuroplasticity, which involves structural and functional brain adaptations in response to changes in environmental life-event, is abnormal in individuals with depression.[18]

CONVENTIONAL TREATMENTS OF DEPRESSION

There are two main methods that are effective in the treatment of depression. One of them is psychological counseling and the other is pharmacotherapy. Cognitive-behavioral therapy (CBT) which is based on changing behavioral and cognitive biases, and psychodynamic therapies (PT) which is revealing the subconscious content of the client, are the two most commonly used approaches in the treatment of depression.[19]

Common pharmacotherapy is originated from the hypothesis that deficiency of monoamine neurotransmitters, such as serotonin, dopamine, and norepinephrine that play a role in the regulation of mood, arousal, and memory.[20] Antidepressants inhibit the reuptake of breakdown of monoamine 5-HT and norepinephrine with 5-HT selective reuptake inhibitors (SSRIs) which represent the most prescribed drug for the treatment of depression.[21]

Although pharmacotherapy has been used as the most effective depression treatment for years, these antidepressants have significant limitations which include long-lasting uses (weeks to months), low response rates (one-third of individuals with depression are treatment-resistant), and adherence problems. Patients who suffer from depression have to use pharmacotherapy for at least 2-4 weeks to get any beneficial effects.[22,23] Also, antidepressants can show some strong adverse effects including weight gain, sexual dysfunction, and cardiovascular problems.[24]

Given some limitations and side effects, innovative treatment approaches for depression are needed. Thus, in this context, a lot of research, particularly on psychedelic drugs, is being conducted as a potential treatment for depression, although there is a bias in this area.[25]

PSYCHEDELICS AS AN ALTERNATIVE TREATMENT

Psychedelics or psychedelic drugs are psychoactive substances that robustly change

perception, mood, and lots of cognitive processes that used by humanity for centuries in ritual settings.[26] Psychedelics include classical serotonergic psychedelics (psilocybin, Lysergic acid diethylamide [LSD], and N, N-dimethyltryptamine [DMT]), entactogens (the serotonin-releasing drug and 3,4-Methylenedioxymethamphetamine [MDMA]), the atypical psychedelic ibogaine, and dissociative anesthetics (N-Nitrosodimethylamine [NDMA] antagonist ketamine).[27]

Psychedelic drugs have been investigated and found promising in other mental disorders such as post-traumatic stress disorder (PTSD),[28] obsessive and compulsive disorder (OCD),[29] substance use disorder,[30] cancer-related anxiety,[31] and suicidal ideation.[32]

Ketamine has also proved as a fast-acting antidepressant with sustained effects by the Food and Drug Administration (FDA) for treatment-resistant depression.[33] It has also been observed that beneficial results have been obtained in the treatment of PTSD[34] and heroin addiction.[35] Ketamine is a drug that is the only anesthetic agent with analgesic, hypnotic and amnesic effects. Although the receptors it binds to have not been fully explained, it has an antagonist effect on N-methyl-D-aspartate (NMDA) receptors throughout the central nervous system (CNS), used as a sedative and anesthetic in individuals and animals.[36]

However, according to a study comparing the effect of ketamine and serotonergic psychedelics on the treatment of depression, psilocybin showed a rapid and persistent antidepressant-like effect in the rat model. In contrast, ketamine only produced a temporary antidepressant-like effect. The results show that psilocybin is a more effective method in the treatment of depression.[24]

The most conducted studies exist for MDMA and psilocybin, which have recently been approved by the FDA as "breakthrough therapies designation" for PTSD and treatment-resistant depression, respectively. Studies about LSD and DMT is observational, yet, there is significant evidence that therapeutic effects in various mental disorders, particularly depression.[37]

NEUROBIOLOGICAL MECHANISMS OF PSYCHEDELIC DRUGS

Psychedelic drugs have the characteristic of changing individuals' behaviors, moods, and perceptions. Imaging studies show that psychedelics affect connecting network functions in various parts of the brain that do not communicate with each other under normal conditions.[38]

5-HT receptors contain the broadest subfamily of G-protein coupled receptors (GPCR). Currently, of 14 different types of 5-HT receptors divided into seven classes of receptors, the 5-HT2A (serotonin 2A/subtype of the 5-HT2) receptor plays a crucial role in the effects of hallucinogens and some mental illnesses with complex etiologies. Although hallucinogens do not only link to 5-HT2A receptors (such as LSD linked to 5-HT receptor subtypes, dopaminergic and adrenergic receptors), activation of 5-HT2A receptors is required to produce hallucinogenesis.[39] It is also effective in certain processes such as mood, learning, memory, sleep-wake cycles, and appetite and also in neurogenesis.[40,41]

Although the 5-HT2A receptor is mainly studied in the Central Nervous System (CNS), also expressed in platelets and the gastro-intestinal tract. 5-HT2A receptor binds to various downstream signaling pathways through the recruitment of a series of cytosolic proteins, including the canonical Gαq protein and the scaffolding protein β-arrestin 2 (βarr2).[39]

Psychedelic drugs as many drugs that target this receptor activate these various G-protein-coupled receptors. However, 5-HT2A is the main receptor responsible for the behavioral effects of psychedelic medicines. LSD more robustly is linked to 5-HT1 and 5-HT2A receptors compared to other serotonergic psychedelics such as psilocybin and DMT. Besides, LSD is linked to adrenergic and dopaminergic receptors that other serotonergic psychedelics are not associated with.[42]

In addition, due to the complex therapeutic effects, deeper research is required. 5-HT 1A, 5-HT 2C, 5-HT4, 5-HT5, 5-HT6, and 5-HT7 are also other serotonin receptors that could be interacted to some degree.[43] DMT and LSD activate trace amine-associated receptors (TAAR1) which are closely associated with psychiatric and neurological disorders.[44] TAAR1 has a modulating effect in areas where dopaminergic, serotonergic, and glutamatergic neurons emerge, reward circuits, limbic networks, cognitive processes, and mood states. Also, it is responsible for the regulation of hormone release, glucose levels, and body weight.[45] DMT also has an agonist effect on the

sigma-1 receptor which are ligand-regulated molecular chaperones whose function contains blocking several voltage-sensitive ion channels.[46]

In a study assuming that psychedelics support structural and functional neural plasticity, it was stated that almost all psychedelics increase the level of neurotrophic factors in neuritogenesis, spinogenesis, and synaptogenesis. In addition, an increase in the number and function of synapses has also been observed. These structural changes caused by psychedelics result from the stimulation of tyrosine receptor kinase B (TrkB), mammalian target of rapamycin (mTOR), and 5-HT2A signaling pathways.[47] Taken together, psychedelic medications can help repair the brain networks of individuals whose prefrontal cortex has been damaged from depression.

Psychedelic drugs, particularly LSD and 2.5-Dimethoxy-4- iodoamphetamine (DOI) which is a synthetic psychedelic have anti-inflammatory and anti-cancer effects.[48,49]

Studies measuring neuroendocrine system-related factors such as the hypothalamus-pituitary-adrenal (HPA) axis and oxytocin have been conducted. LSD, psilocybin, and DMT increase serum cortisol and adrenocorticotropic hormone (ACTH). Oxytocin levels are low in individuals with depression, studies have shown that LSD increases oxytocin levels.[50]

Although many other compounds are used as drugs in the treatment of various psychiatric diseases and also alter consciousness, this study will discuss the serotonergic psychedelics which are LSD,[51] psilocybin,[52,53] and DMT,[54,55] as considered to be the most effective in the treatment of depression.

LYSERGIC ACID DIETHYLAMIDE (LSD)

LSD was first discovered by Albert Hofmann in 1938. It is one of the classical psychedelics which are psychoactive substances that typically produce perceptual distortions and change in states of consciousness, mainly by agonistic action at the serotonin 5-HT2A receptor.[26] Some experimental researches showed that LSD increases positive mood, social behavior, emotional empathy and reduces negative emotional states.[56,57] LSD is the strongest psychedelic that has very slow dissociation kinetics at the 5-HT2A receptor and therefore long-lasting effects.[58]

Mental effects of LSD include distortion of the sense of time and identity, changes in in-depth and time perception, visual hallucinations, sense of euphoria, distorted perception in senses of visual, auditory, touch and smell, and body image and delusions.[59] "Bad trip", defined as acute anxiety, dysphoria, and confusion which can lead to unpredictable behavior in uncontrolled settings and exacerbation of psychotic disorders or the development of long-term psychotic reactions that may be related to the individual's previous predisposition are adverse effects. Also, in terms of physiological effects, increasing blood pressure and heart rate is another possible adverse effect of LSD.[60,61]

The first research on using LSD in treating depression was conducted on 15 individuals suffering from depression in 1952 by Savage. Improvement acquired using LSD therapy was no greater than without its use. However, therapeutically valuable data into unconscious processes were obtained.[62]

LSD has been used from the 1950s to the 1970s to achieve behavioral and personality changes as well as treatments of various disorders such as anxiety, depression, psychosomatic diseases, and addiction.[52] Some researches showed that LSD could decrease pain, anxiety, and depression in patients with cancer.[63]

Some researches indicated that LSD has a therapeutic potential even with lower doses and without the psychedelic experience. Some of the reviewed researches showed that positive effects on cognitive and affective processes that are dysfunctional on individuals suffering from depression.[64]

PSILOCYBIN

Psilocybin is hallucinogenic mushrooms that structurally belong to the group of tryptamine hallucinogens and are structurally related to serotonin. Its chemical compounds have a similar structure to LSD. In the history of psilocybin, It was used for ritual in Mexico 3000 years ago, and regionally its use is continuing today. In the 1960s, experimental research on mental disorders was conducted using psilocybin. Nowadays, psilocybin is one of the most used psychedelics due to its safety and long-time positive effect.[65,66]

It is known that 5-HT1A and 5-HT2A receptors have an important role in the pathophysiology of dysfunctional emotional biases. In the light of those

researches, Kometer and his colleagues investigated the effects of psilocybin on facial recognition, goal-directed behavior, and mood state in 2012. Psilocybin increased positive mood and weakened recognition of negative facial expression. Also, psilocybin has been found to have a positive effect on goal-directed behaviors.[56] Psilocybin has a strong effect on mood contrast than other drugs. Bernasconi and his colleagues researched in 2014 to determine neurophysiological modulation induced by psilocybin to emotional face processing. The result showed that psilocybin affects the neuronal correlates of emotional face processing, consistent with a modulation of the top-down control.[67]

Research conducted on 12 individuals suffering from severe depression has provided strong evidence that reduction in depression severity at 1 week was sustained in the majority for 3 months after psilocybin use. Also, any unexpected or serious adverse events were not observed.[68]

AYAHUASCA (CONTAINS DMT)

Ayahuasca is a brew obtained from a combination of the plant of Psychotria Viridis which has DMT, and the plant of Banisteriopsis Caapi which contains β-carboline (harmine, harmaline, and tetrahydroharmine) that act as reversible monoamine oxidase inhibitors (MAO)-A. For ages, it has been utilized in shamanic rituals and for therapeutic purposes.[69]

The researchers have indicated the potential benefits of ayahuasca and DMT in mood disorders.[51] Several studies indicated that harmine has an antidepressant effect.[70,71] It has shown decreased stress parameters in the hippocampus, a structure related to mood regulation.[72]

The first controlled trial has been conducted to test the antidepressant effects of ayahuasca which is the psychedelic substance in 29 patients with treatment-resistant depression in 2018. The Montgomery-Asberg Depression Rating Scale (MADRS) and Hamilton Depression Rating Scale (HAM-D) have been used to assess changes in depression severity. Compared to placebo, HAM-D scores on the 7th day were significantly lower in individuals treated with ayahuasca, and MADRS scores were significantly decreased in the group of individuals treated with ayahuasca at all times (at days 1, 2, and 7).[54]

Although some researches indicated that ayahuasca has effectiveness in the treatment of depression, there is a great need to conduct preclinical and clinical randomized controlled studies to determine its clinical and pharmacological effects and safety. Also, more detailed researches need to be done about the adverse effects of psychedelics, despite the fact that it appears to relatively mild.[73]

PSYCHEDELIC-ASSISTED PSYCHOTHERAPY (PAP)

Psychedelic-assisted psychotherapy (PAP) has been defined as using ketamine, MDMA, psilocybin, LSD, and ibogaine as part of detailed psychotherapy sessions under the control of therapists.[74] Although there are several methodologies used in psychedelic-assisted psychotherapy, psycholytic therapy, and psychedelic therapy are two of the most commonly used among them.[75,76]

Psycholytic therapy, which emerged in Europe in the 1950s, refers to a kind of psychoanalytically informed talk therapy integrating with the administration of low doses of LSD (30-200 mg) over several sessions. The sessions were believed to give patients deeper access to the unconscious for emotional relaxation.[77]

In psychedelic therapy developed in the United States, high doses (250 mg LSD) were used to create an "overwhelming and transcendent experience" and the aim was novel insights into the patient's condition. Psychedelic-assisted psychotherapy consists of three sessions which are preparatory, medication, and integration. The aim of these three parts is to prepare the patients for the psychedelic sessions and set the therapeutic alliance. The therapist acts as a guide to help the patient gain insight during the psychedelic session safely and convert the process of that experience into meaningful, long-lasting change. Before given the drugs, preparation and orientation to the therapy are crucial.[78]

The session should conduct in a well-decorated and comfortable environmental setting that making the patients feel familiar. After drug ingestion, the therapist supports the patient to focus and trust on his or her inner healing intelligence. Because the patient needs to accept the belief that the power to heal is hidden within her. Several tools can be used in the therapeutic setting such as listening to music, in particular instrumental evocative music,[79] wearing eyeshades, or breathing technique.[80,81]

Under the drug effect, the therapist listens to the patient carefully and seeks to increase the benefits of the inner experience. The goal should be to maintain and strengthen the bonds of trust, safety, and openness between the therapist and the patient. Finally, the therapist works with the patient to integrate this experience into meaningful long-term change by identifying the insights that arise during the psychedelic session and interpreting the thoughts.[37]

It is unknown that what is providing change is the psychedelic medicine itself, the psychedelic-assisted psychotherapy, or drug-facilitated improvement in the therapeutic alliance.[77] So, more studies focusing on psychedelic-assisted therapy are required.

Conclusion

The number of individuals affected by depression is increasing day by day. According to the World Health Organization (WHO), current estimates suggest that depression will be one of the global burdens of disease by 2030. In addition to the treatment costs of people affected by depression, it may cause economic difficulties in countries due to occupational inadequacy. So, future studies on alternative treatments that conduct to modern standards are necessary.

Psychedelics have been used for shamanic rituals for centuries. It has proven its effectiveness as a robust drug today. Studying psychedelic drugs for the treatment of depression can be seen as taboo because we do not fully describe the changes in the human mind, perception, mood, and behavior neurobiological, or because we know its potential to be used as a pleasurable substance. However, FDA approval of psilocybin for the treatment of depression has shown that it can be used as a potential drug for mental disorders. Although generally observational study is conducted on LSD and ayahuasca, their therapeutic effects in various mental disorders are robustly promising for the future.

Nevertheless, more research is necessary to evaluate the safety and effectiveness of psychedelic treatments on depression to inform potential future use in psychiatric practice.

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