Serotonergic Hallucinogens in Depression Treatment

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Depressive disorder is a demanding and common condition affecting more than 264 million people worldwide [1]. Despite many studies, the etiology of this disease remains unknown [2]. Some psychedelics, especially psilocybin, demonstrated an ability to reduce depressive symptoms as measured by several psychological scales, which was often sustained for months after the last psychedelic session.

Keywords: psychedelics ; depression ; serotonergic hallucinogens ; psilocybin ; MDMA ; LSD ; DMT

1. Introduction

1.1. Depression in the General Population

Some factors are strongly associated with a higher risk of developing depression, including environmental factors like emotional, physical, and sexual abuse; genetic and epigenetic factors; and organic changes in the central nervous system, especially in the hippocampus. These factors can affect the neurobiological stress-responsive systems, resulting in neuroinflammation and altered neurotransmission [1]. The biological dysfunctions produced by these factors can also have a great impact on physical health and are associated with a higher risk of developing various conditions, such as heart disease, disability, diabetes mellitus, obesity, and cancer [2]. However, the most pressing clinical concern is suicide, a direct cause of death in patients with depressive disorders, as the pooled lifetime prevalence of suicide attempts in depressed patients is estimated to be 27–34%, which is almost 20 times greater than in general population [3][4].

1.2. Current Treatment Methods for Depression and Their Limitations

Currently, the two main treatment methods for depression are psychotherapy and pharmacotherapy. There are various types of psychotherapies with proven efficacy, including cognitive-behavioral therapy, behavioral activation therapy, problem-solving therapy, and interpersonal therapy [5]. Pharmacotherapy is the first-line therapy, and it is based on antidepressants, such as monoaminergic reuptake inhibitors and tricyclic antidepressants [6]. Despite proven efficacy, a high percentage of patients treated with these drugs exhibit treatment-resistant depression [7]. Indeed, it is estimated that only about 30–40% of patients with depression, especially those diagnosed with major depressive disorders (MDD), acquire full remission with first-line therapy, and about one third of patients do not achieve remission even if treated with as many as four different antidepressants [8]. Antidepressant treatment is also associated with a wide array of adverse events [9]. Although current research suggests that fluoxetine, a serotonin reuptake inhibitor, is likely the only effective antidepressant for children and adolescents, the WHO discourages antidepressant use in children and recommends against its use as a first-line treatment in adolescents [10][11]. Often both psychotherapy and pharmacotherapy are combined. The main advantages of non-pharmacological treatments are their safety profile and low incidence of adverse effects. However, the quality of the evidence indicates their efficacy is poor [12]. There are other methods used for the treatment of depression, such as electroconvulsive therapy, brain stimulation, physical activity, and even biological treatment [13][14][15][16][17]. Among brain stimulation techniques worth mentioning are cranial electrotherapy stimulation (CES) and repetitive transcranial magnetic stimulation (rTMS), both FDA-approved for major depressive disorder [14][18][19][20]. Currently, many researchers are examining the potential of using serotonergic hallucinogens to reduce depressive symptoms.

1.3. Serotonergic Hallucinogens as a Potential Treatment for Depression

Hallucinogens are a group of psychoactive chemicals with various mechanisms of action that cause significant alterations in the central nervous system, resulting in changes in human consciousness [21]. These substances, such as d-lysergic acid diethylamide (LSD), dimethyltryptamine (DMT), and psilocybin, can act on serotonin 5-HT2A receptors as agonists. More recently, chemists have developed new “designer drugs”, such as 3,4-methylenedioxymethamphetamine (MDMA), that stimulate the release of serotonin, dopamine, and norepinephrine and can inhibit their reuptake by blocking, for

example, the serotonin transporter [22]. Hallucinogens may also have additional actions at other serotonin receptors (particularly 5-HT1A and 5-HT2C) and can act on other neurotransmitter systems [23][24]. These drugs can also exhibit rapid and long-lasting antidepressant and anxiolytic effects [25]. It also seems as if the experience of an altered state of consciousness produced by these agents has a great impact on the final therapeutic effect [26]. It should also be noted that hallucinogens do not lead to dependence, as these drugs do not directly influence the dopaminergic system [27].

2. Serotonergic Hallucinogens in Depression Treatment

2.1. Psilocybin

There were four studies [28][29][30][31] that evaluated the efficacy and safety of using psilocybin in the treatment of depression symptoms. The research protocol of each study was similar and consisted of two 6-hour experimental sessions spaced a few (2–7) weeks apart. The sessions were conducted in a room designed to be aesthetic and appealing to the participants. During the sessions, the participants were encouraged to lie in bed and listen to preselected music. They were also monitored by health professionals, who supported and encouraged the participants to relax, trust, and follow the experience and helped them to sum up their thoughts and feelings after the sessions. After the sessions, the patients discussed their subjective cognitive, affective, and psychospiritual experiences. All four studies were cross-over designs, and patients acted as their own controls. The characteristics of each study are presented in **Table 1**.

Table 1. Characteristics of reviewed studies on the use of MDMA, DMT, and LSD in the treatment of depression (Randomized Controlled Trial study, RTC).

No.	Studies' Authors, Year	Substance/Test Group	Substance/Control Group	Comorbid Condition	No. of Participants	Used Questionnaires to Measure Depressive Symptoms
1	Kraehenmann R et al., 2015 [28]	Psilocybin, 0.16 mg/kg	Lactose	Healthy volunteers	25	PANAS, STAI
2	Ross S et al., 2016 [29]	Psilocybin, 0.3 mg/kg	Niacin, 250 mg	Advanced cancer	29	HADS, BDI, STAI, MEQ 30
3	Griffiths RR et al., 2016 [30]	Psilocybin, 22 or 30 mg/70 kg	Psilocybin, 1 or 3 mg/70 kg	Advanced cancer	51	GRID-HAMD-17, BDI, HADS, STAI
4	Carhart-Harris R et al., 2021 [31]	Psilocybin, 25 mg versus Escitalopram, 10–25 mg	Psilocybin 1 mg, placebo	Major depressive disorder	66	QIDS-SR-16
5	Ot'alora G M et al., 2018 [32]	MDMA, 125 or 100 mg	MDMA, 40 mg	PTSD	28	BDI
6	Mithoefer MC et al., 2019 [33]	MDMA, 75–125 mg	MDMA, 0–40 mg	PTSD	103	BDI
7	Wolfson PE et al., 2020 [34]	MDMA, 125 mg	Lactose, 125 mg	Life-threatening illness	18	BDI, MADRS
8	Bershad AK et al., 2019 [35]	LSD, 6.5–26 µg	Lactose	Healthy volunteers	20	POMS

Abbreviations: 5D-ASC—5-Dimension Altered States of Consciousness; BDI—Beck Depression Inventory; BPRS—Brief Psychiatric Rating Scale; DASS-21—Depression, Anxiety, Stress Scale 21; DMT—dimethyltryptamine; GRID-HAMD-17—GRID-Hamilton Depression Rating Scale; HADS—Hospital Anxiety and Depression Scale; MADRS—Montgomery–Asberg Depression Rating Scale; MDMA—3,4-methylenedioxymethamphetamine; MEQ 30—Mystical Experience Questionnaire; LSD—D-lysergic diethylamide; PANAS—Positive and Negative Affect Schedule; POMS—Profile of Mood States; STAI—State-Trait Anxiety Inventory; QIDS-SR-16—Quick Inventory of Depressive Symptomatology-Self-Report.

The study of Kraehenmann et al. focused on the effects of psilocybin on amygdala reactivity to negative stimuli obtained from the International Affective Picture System (IAPS). The study involved 25 healthy volunteers who, in large part, had no history of previous hallucinogen use. The participants received either psilocybin (0.16 mg/kg) or placebo (lactose) in two experimental treatment sessions. During the sessions, the mood was assessed, and functional magnetic resonance imaging (fMRI) was used to evaluate the effects of psilocybin on amygdala activity during emotion processing. The results

showed that psilocybin reduced amygdala reactivity to negative and neutral stimuli and improved the mood of healthy volunteers, as confirmed by the Positive and Negative Affect Schedule (PANAS) scores. These findings suggest that psilocybin may normalize the amygdala hyperactivity and negative mood states associated with depression [28].

2.2. MDMA

The Ot'alora et al. study involved 28 patients with chronic PTSD, of which nearly half (42.9%) had been diagnosed with MDD and 25% with depression. The lifetime Suicide Severity Rating Scale (SSRS) showed that 27/28 (92.6%) patients had suicidal ideation, and 8/28 (28.6%) exhibited suicidal behavior. During two eight-hour sessions spaced a month apart, patients received either an active (125 or 100 mg) or a comparator (40 mg) dose of MDMA. Changes in depressive symptoms, as measured by the BDI, showed approximately equivalent decreases across the groups. However, after an additional third open-label session where all participants received 100 mg or 125 mg MDMA, there was a significant improvement in the BDI at the 12-month follow-up compared to the baseline (7.3 points vs. 27.8 points) [32].

2.3. LSD

Bershad et al. conducted a double-blind study where 20 healthy volunteers received 0, 6.5, 13, or 26 µg of LSD, each in one out of four 8-hour sessions. Subjective mental health state was measured at the baseline, at 30 to 90 min intervals after receiving the drug, and at the peak of the drug effect. The sessions were spaced at least 7 days apart. The Profile of Mood States (POMS) was used to measure anxiety and depression symptoms. The POMS anxiety scale revealed that the LSD effect correlated with the dose administered and that there was a trend for the highest dose to increase ratings. However, for the POMS depression scale, the effects of LSD did not reach statistical significance [35].

2.4. Open-Label Studies

Five studies revealed that the administration of 10–25 mg psilocybin in patients with treatment-resistant MDD significantly reduced depressive symptoms and that this effect persisted for 5 weeks–5 months as measured by the QIDS, BDI, STAI-T and Snaith-Hamilton Pleasure Scale (SHAPS) [36][37]. fMRI images also showed that the amygdala response to emotional stimuli increased after psilocybin intake, which can be related to an enhanced ability to face and work through negative emotions, an increase in functional connectivity between the amygdala and prefrontal cortex and the occipital-parietal cortices, and a revival of emotional responsiveness [38][39].

Table 2. Characteristics of reviewed studies on the use of MDMA, DMT, and LSD in the treatment of depression (open-label studies).

No.	Studies' Authors, Year	Substance	No. of Participants	Comorbid Condition	Results
1.	Carhart RL et al., 2016 [36]	Psilocybin, 1. dose: 10 mg, 2. dose: 25 mg	12	Major depression disorder (MDD) (moderate to severe degree, treatment-resistant)	A significant reduction in depressive symptoms lasting up to 3 months after 2. dose, relative to the baseline, measured by: QIDS (10.0 vs. 19.2) BDI (15.2 vs. 33.7) STAI-T (54.8 vs. 70.1) SHAPS (2.8 vs. 7.5)
2.	Carhart RL et al., 2017 [37]	Psilocybin, 1. dose: 10 mg, 2. dose: 25 mg	19	MDD (treatment-resistant)	A significant reduction in depressive symptoms lasting up to 5 weeks, measured by QIDS-SR16, were observed in 18 patients (95%) (mean change: −9.2); 9 patients (47%) met criteria for response (≤50% reductions). Reduced depressive symptoms were correlated with decreased amygdala CBF in fMRI.
3.	Carhart RL et al., 2018 [40]	Psilocybin, 1. dose: 10 mg, 2. dose: 25 mg	19	MDD (severe, treatment-resistant)	A significant reduction in depressive symptoms lasting up to 6 months, relative to the baseline, measured by: QIDS-SR16 (p = 0.0035) BDI (19.5 vs. 34.5) STAI (53.8 vs. 68.6)
4.	Roseman L et al., 2018 [38]	Psilocybin, 1. dose: 10 mg, 2. dose: 25 mg	20	MDD (moderate to severe, treatment-resistant)	Post-treatment increased amygdala responses to emotional stimuli in fMRI suggest that psilocybin allows to confront and work through negative emotions (induced by showing fearful and happy faces).

No.	Studies' Authors, Year	Substance	No. of Participants	Comorbid Condition	Results
5.	Mertens LJ et al., 2020 [39]	Psilocybin, 1. dose: 10 mg, 2. dose: 25 mg	19	MDD (moderate to severe, treatment-resistant)	Post-treatment increase in functional connectivity between the amygdala and ventromedial prefrontal cortex to occipital-parietal cortices in fMRI during face processing.
6.	Uthaug MV et al., 2020 [41]	DMT, 17–61 mg	10	-(Healthy volunteers)	Significant reduction of depressive symptoms, sustained at 7-day follow-up, measured in DASS-21.

Abbreviations: BDI—Beck Depression Inventory; CBF—Cerebral Blood Flow; DASS-21—Depression, Anxiety, Stress Scale 21; fMRI—functional Magnetic Resonance Imaging; QIDS—Quick Inventory of Depressive Symptoms; QIDS-SR16—16-item Quick Inventory of Depressive Symptoms; SHAPS—Snaith-Hamilton Pleasure Scale; STAI-T—State-Trait Anxiety Inventory.

2.5. Adverse Events after Hallucinogen Use

Five out of fourteen studies did not include any information about adverse effects [28][35][40][38][39]. The reported adverse events were divided into five categories: psychological, neurological, cardiovascular, gastroenterological, and general. The most common psychological adverse events were transient anxiety [29][32][33][36][37][41] and psychological discomfort [30], while the most common neurological events were headache [29][31][32][33][36][37] and, for MDMA administration, dizziness and jaw clenching [32][33]. In the psilocybin studies, there were also gastroenterological adverse events noted, most commonly nausea and/or vomiting [29][30][31][36][37]. Most researchers measured blood pressure and heart rate during psilocybin studies and observed an elevation in blood pressure [29][30] and heart rate [29]; however, these increases were often not considered adverse events [31][32][33][34][35][36][37]. There were also some general adverse events noted, mostly in MDMA studies, including fatigue [31][32][33] and a lack of appetite [32][33][34].

3. Summary

Some hallucinogens are effective at reducing depressive symptoms and indicate that these agents may be used in the future as a novel treatment for depression. The administration of hallucinogens, especially psilocybin, results in a sustained reduction in depressive symptoms with an absence of serious adverse effects. It is worth mentioning the importance of the psychedelic experience itself and realizing that it can often be intense and overwhelming for a patient. Thus, the presence of a properly qualified monitor-therapist throughout the experience is necessary to ensure a positive result from each session. Compared to currently available methods, psychedelic therapy seems to be safer than the chronic use of antidepressant drugs but requires more time than regular therapy, as the effects of psychedelics can last up to 12 h. However, antidepressants and psychotherapy should remain first-line treatments, as their efficacy and safety are validated in clinical practice and available literature.

There are a few limitations of the existing studies on psychedelics. First, the sample size used was small and often consisted of healthy volunteers rather than patients suffering from actual conditions. Due to the characteristic and inimitable effects of these drugs, it has also been difficult to construct a study with adequate double blinding. To overcome this problem, some researchers have used a low, "placebo-like" dose of a substance for the control group, which can produce some effects that may not be obvious to the participants.

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