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PSYCHEDELICS IN PSYCHIATRY - OVERVIEW OF PSILOCYBIN RESEARCH

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ABSTRACT

Introduction: Recently, there has been a significant increase in interest in the use of psychedelics for various psychiatric conditions. Psilocybin is receiving particular attention as a psychoactive substance with significant therapeutic potential. Recent research focuses on its possible benefits in the treatment of major depressive disorders (MDD) and anorexia nervosa (AN).
Purpose of the study: This study aims to investigate the therapeutic potential of psilocybin in treating MDD and AN by analyzing its mechanism of action, clinical trials results and further implications of PAT.
Materials and methods: An overview of 26 articles sourced from PubMed and open-access databases was conducted, with a focus on randomized controlled trials, neurobiological mechanisms and also exploratory research.
Conclusions: Psilocybin and PAT demonstrated significant antidepressant effects, enhancing neuroplasticity, connectivity and cognitive flexibility. While evidence in MDD is significantly more established, preliminary findings in AN are promising, but still require further controlled clinical trials. Psilocybin represents a novel approach to treatment of MDD and AN.

KEYWORDS

Psilocybin, Psilocybin-Assisted Psychotherapy, Major Depressive Disorder, Anorexia Nervosa

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1. Introduction

Psilocybin, the psychoactive compound found in certain hallucinogenic mushrooms, is currently undergoing a significant renaissance in clinical research after years of regulatory suppression [1].

Historically used in spiritual practices and cultural rituals, psilocybin is now being studied for its therapeutic potential in treating certain treatment-resistant neuropsychiatric conditions. Psilocybin-assisted psychotherapy (PAT) is gaining attention for its promising effectiveness in major depressive disorders (MDD) and anorexia nervosa (AN). MDD and AN both are often resistant to conventional treatment, which makes them potential targets for novel therapies.

PAT has been granted" breakthrough therapy" status in treatment of MDD [2, 3]. The field of PAT has significantly advanced in treatment of MDD and other neuropsychiatric conditions, while research focusing on its effects in eating disorders has lagged behind. The reason for that is partly due to the limited understanding of the underlying mechanisms of eating disorders, making it challenging to explore the exact pathway through which psychedelics may have therapeutic effect [4]. Nevertheless, several pathways have been proposed, such as direct serotonergic action via 5-HT2A receptor agonism, modulation of large-scale brain networks affecting neuroplasticity and connectivity and enhancement of cognitive flexibility [5]. Adding to that PAT also has a potential to address core challenges of eating disorders such as distorted body image, dysfunctional reward response and rigid cognitive-behavioral patterns [6-9].

2. State of Knowledge

Psilocin is the active metabolite of psilocybin, which essentially activates the serotonin 2A receptor (5-HT2AR) in the frontal cortex, responsible for triggering psychedelic response in humans. Research suggests that activation of the receptor also has a beneficial effect, resulting in increased glutamine neurotransmission, thereby modulating prefrontal network activity and potentially leading to an increased AMPAR/NMDAR ratio. This signaling cascade possibly promotes brain-derived neurotrophic factor (BDNF) and mammalian target of rapamycin (mTOR) signaling, which in turn upregulates the synthesis of synaptic proteins and promotes synaptogenesis [10, 11]. The increased neuroplasticity is linked to enhanced cognitive flexibility, which means individuals may become more open to novel experiences, engage in more flexible thinking, hence experience a reduction in ruminative or obsessive thought patterns often seen in mood disorders [12].

Randomized controlled trials on psilocybin-assisted treatment of major depression disorder (MDD) unveiled that at 12-month follow-up 75% of participants met criteria response (at least 50% reduction in GRID-HAMD score) and 58% were in remission (GRID-HAMD score 7 or less). Psilocybin was administered within two doses, of 20mg/70kg and 30mg/70kg with a two-week interval. Participants who received immediate psilocybin therapy showed greater improvement in depression severity, compared to those in delayed treatment [13, 14]. Notably, a little as one dose (25 mg), significantly improved patient-reported outcomes in individuals with treatment-resistant depression [15]. Although data demonstrate the substantial and sustained antidepressant effect of psilocybin therapy, extended research on larger and more diverse populations is required to establish the role of psilocybin in MDD treatment. Another randomized controlled trial assessing the effect of psilocybin therapy versus escitalopram on'maladaptive' cognitive biases relevant to the construct of depression revealed that psilocybin therapy led to a significant increase in self-reported optimism six weeks after treatment, whereas escitalopram did not show a significant change in optimism. Both psilocybin and escitalopram reduced depressive symptoms, but psilocybin showed a significantly greater decrease. Overall psilocybin was associated with improvements in achievement, dependency and self-control and led to significantly greater increases in psychological flourishing. Researchers emphasize that a six-week study period might not have been long enough for escitalopram to reach its full therapeutic effect. Nevertheless findings support the idea that psilocybin improves cognitive biases in patients struggling with depression [16]. Separate study investigated psilocybin potential in suecide prevention using pharmacological and molecular docking. Authors identified four primary targets: HTR2A, HTR2C, HTR7 and PRKACA - pivotal for

psilocybine's therapeutic action. These targets are specifically associated with serotonergic synapse and calcium signaling pathways, connected with suicidal behaviour [17]. Trials conducted on rodents, support the fact that psilocybin may alleviate anhedonia - one of the main symptoms of depression, and present an anxiolytic-like effect in treated animals. The proposed mode of action considered increased expression and function of serotonin-2A receptor (5HT2AR) in the brain cortex [10]. A distinct study indicated that psilocybine can impact gut-brain axis, which involves the bidirectional connection amongst the nervous, endocrine and immune system, as well as gut microbiota and its metabolites. Gastrointestinal neuroendocrine system, especially enterochromaffin cells (EC) and gut bacteria are responsible for production of approximately 90-95% of the body's serotonin (5-HT). It is suggested that low consistent doses of psilocybin can indirectly alter 5-HT and other neurotransmitter production, together with activation of afferent vagus endings by changes in gut microbiome. Gut dysbiosis, increased intestinal permeability and gut inflammation, predispose individuals to stress and anxiety leading directly to mood disorders [12, 18].

Anorexia nervosa (AN) is the most fatal of all psychiatric conditions. Moreover it is linked with high treatment dropout rates and low remission rates, therefore urgent need for novel therapeutic strategies, such as psychedelic drugs [19]. By enhancing cognitive flexibility and modifying reward processing psilocybin shows potential as a treatment for anorexia nervosa. These effects are mediated by interactions between serotonin and dopamine system in prefrontal cortex and nucleus accumbens. Studies have shown that psilocybin can increase extracellular dopamine in certain brain regions, yet further research is needed to investigate the mechanism of this process [20, 21]. Peck et al. presented a study in which a single dose of 25-mg of psilocybin combined with psychological support was administered to 10 adult females with AN. Results showed that 90% felt more positive about life and 70% reported a shift in personal identity [22]. Patients with AN struggle with consequences of malnutrition, including bradycardia and hypotonia, which is why they are more likely to tolerate psilocybin adverse effects, like tachycardia and hypertension, than other clinical populations [23].

Insight from psilocybin experience can provide a deeper understanding of the subjective effect of psilocybin. Understanding these subjective experiences can be crucial for tailoring an individual psychotherapy as well as building a stronger bond by increasing clinicians' comprehension of their patients' internal experience. This suggests that the subjective psychological effect of psychedelic experience may play a fundamental role in recovery from mental illness [24].

3. Results

Progress in research on the usefulness of psilocybin in the treatment of mental disorders is undeniable and rapidly advancing. In randomized controlled trials for MDD, an overwhelming majority of participants improved at a 12-month follow-up, with 75% responding criteria and 58% achieving remission [13, 14]. Even a single dose of psilocybin (25 mg) yielded large improvements in patient-reported outcomes in treatment-resistant depression [15]. Two-photon microscopy pioneering experiments have demonstrated that a one-time dose of psilocybin (1 mg/kg) induces a roughly 10% increase in the size and density of dendritic spines on layer V prefrontal cortex pyramidal neurons in mice. Structure changes are rapid – within 24 hours of drug dosing – and long-lasting for at least one month. Longitudinal analysis indicates that the enhancement of spine density results from an increased rate of formation with no alteration in the rate of elimination. The most significant aspect of psilocybin-induced neuroplasticity is its persistence. Follow-up studies conducted 34 days after psilocybin administration showed that about 35% of the newly established dendritic spines remained, and it was suggested that some of them develop into mature synapses [25]. The long-term stability could be a structural foundation for the long-term therapeutic effects of psilocybin. Comparison trials suggest psilocybin therapy leads to greater increases in self-reported optimism and a greater reduction in depressive symptoms compared with some conventional antidepressants like escitalopram [16]. Mechanistic analyses have suggested that the mental health improvements following psilocybin treatment—such as higher well-being, reduced depressive severity, suicidal ideation, and trait anxiety – occur through a reduction in experiential avoidance. This was not observed with escitalopram. Explanatory analyses also suggest that the improvement in mental health through reduced experiential avoidance is also mediated through a greater sense of connectedness [26]. Psilocybin can also have a beneficial effect on maladaptive cognitive biases in depression [16]. In anorexia nervosa, preliminary research demonstrated psilocybin, when combined with psychological support, can yield positive changes in outlook and personal identity [22]. The data suggests psilocybin's usefulness lies in enhancing cognitive flexibility and changing reward processing, which may address core challenges in AN, such as distorted body image and inflexible thinking.

4. Discussion

The renewed interest in psychedelic-assisted therapy (PAT), especially with psilocybin, reflects a growing shift in how psychiatric conditions are conceptualized and treated. Current literature highlights psilocybin's therapeutic promise, particularly in mood disorders like major depressive disorder (MDD), and, more cautiously, in eating disorders such as anorexia nervosa (AN) [8, 15, 16].

Unlike conventional antidepressants, which often require prolonged daily use, psilocybin has been associated with rapid symptom relief following only one or two administrations [4, 16]. This observation suggests a distinct mechanism involving activation of the 5-HT2A receptor, modulation of glutamatergic signaling, and enhanced neuroplasticity [11, 12, 24]. Improvements in cognitive flexibility and self-perception reported in several studies further support this proposed biological pathway [17, 24].

While evidence supporting psilocybin's role in MDD continues to strengthen, its application in AN remains in the early stages. Individuals with AN often face limited treatment options and high dropout rates [7]. Early-phase studies indicate possible improvements in body image and emotional regulation following psilocybin therapy, but the generalizability of these results is constrained by small sample sizes and the lack of randomized controlled trials. Additionally, physiological vulnerability in this population—such as cardiovascular instability—necessitates cautious clinical oversight [6, 8].

Several limitations should be considered. Many existing studies involve highly selective participant groups, frequently excluding individuals with psychiatric or medical comorbidities. The therapeutic context itself—encompassing psychological support, set, and setting—makes it difficult to isolate the pharmacological effect of psilocybin from its psychosocial components [15, 16].

One area attracting increasing attention is the interaction between psilocybin and the gut-brain axis, including possible modulation of microbiota and serotonin-producing enterochromaffin cells [9]. While this remains a hypothesis, it could be especially relevant in disorders where gastrointestinal and emotional symptoms intersect—such as in AN—suggesting potential for more holistic therapeutic approaches in the future.

Despite encouraging outcomes, psilocybin remains classified as a Schedule I substance in many jurisdictions, and significant regulatory and ethical challenges remain. For vulnerable populations like those with AN, establishing clear safety frameworks, therapist training, and integration protocols will be essential [5, 6].

Altogether, the data point to psilocybin-assisted therapy as a paradigm shift in psychiatric care. While its efficacy in depression is increasingly supported, its role in other disorders such as AN is still being explored. Future studies should aim to expand sample diversity, examine long-term outcomes, and refine treatment models to safely harness the therapeutic potential of psychedelic compounds.

5. Conclusions

Psilocybin, a psychoactive compound found in hallucinogenic mushrooms, is gaining popularity due to research into its potential for treating neurological and psychiatric disorders. Randomized controlled trials on the treatment of major depression have shown improvements in symptom severity with psilocybin-assisted therapy. Even a single dose has shown potential in improving outcomes reported by patients with treatment-resistant depression. Although the therapeutic benefits of psilocybin have already been demonstrated, further studies involving larger and more diverse populations are necessary to determine the role of this substance in depression treatment. In another randomized trial comparing psilocybin therapy to escitalopram therapy, psilocybin treatment led to increased self-reported optimism even six weeks after treatment, whereas escitalopram did not show such an effect. Both compounds show potential in reducing depressive symptoms; however, psilocybin demonstrates a greater decrease and is also associated with improved self-control. Animal studies have shown that psilocybin may alleviate anhedonia and exhibit anti-anxiety effects. Another study indicated that psilocybin may influence the gut-brain axis. The neuroendocrine system of the gastrointestinal tract is responsible for producing the neurotransmitter serotonin. It is suggested that low, consistent doses of psilocybin may indirectly affect serotonin production. Conditions associated with increased intestinal permeability and gut inflammation – which predispose individuals to stress and anxiety – can directly contribute to mood disorders. Another area where psilocybin has shown potential is in the treatment of anorexia. Anorexia nervosa is considered the deadliest of all psychiatric disorders and is associated with a high rate of treatment dropout, prompting the need for new therapeutic strategies. Some studies have found that psilocybin can increase extracellular dopamine levels in specific brain regions. This compound may aid in treating anorexia by enhancing cognitive flexibility and modifying reward processing. Despite these early findings, further research on larger populations is necessary. Psilocybin appears to hold therapeutic potential that could prove to be groundbreaking in the treatment of neuropsychiatric disorders.

Conflict of Interest Statement: No conflicts of interest to declare.

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