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Psilocybin's Emerging Role in Combating Depressive Disorder

Wzrastająca Rola Psylocybiny w Zwalczaniu Zaburzeń Depresyjnych

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Abstract:

In this review paper, we delve into the potential applicability of psilocybin - a naturally synthesized psychedelic substance found within select species of fungi, as a prospective avenue for depression treatment. Depression, a widespread psychological malady affecting countless individuals across the globe, often proves stubborn against existing treatment modalities, necessitating exploration into new options. The spotlight has increasingly been cast on psilocybin, thanks to its promising therapeutic capacities for a spectrum of mental health disorders, notably including depression. This article dissects the operational mechanisms of psilocybin, referencing germane clinical trials, and weighing the prospective risks and rewards related to its usage.

Pooled findings from an array of clinical studies hint at the possibility of psilocybin furnishing swift and lasting advantages for managing depression and similar disorders. Trial participants who underwent a combined regimen of psilocybin and psychotherapy recorded enduring alleviation in their anxiety and depressive symptoms. Psilocybin has been observed to trigger modifications in neural activity, predominantly in the brain's default mode network (DMN) and the prefrontal cortex (PFC). These alterations have been correlated with a decrease in self-oriented cognitive processes, an uptick in positive emotional states, and the facilitation of neuroplasticity. When compared with standard antidepressant medications, the symptomatic improvements seen with psilocybin were largely equivalent. Preclinical investigations have also underlined psilocybin's potential in augmenting neural plasticity and neurogenesis, thus hinting at its possible utility in the fields of neurosurgery and neurooncology.

Słowa kluczowe: psilocybina, depresja, depresja odporna na leczenie

Introduction:

Depression stands as a predominant mental health issue, impacting countless individuals globally and significantly impairing one's quality of life and holistic wellness. As outlined by the World Health Organization (WHO), depression holds the notorious distinction of being the principal driver of disability on an international level. (1) Close to 3.8% of the global populace grapples with depression, encompassing 5% of the adult demographic

(comprising 4% of males and 6% of females) and 5.7% of individuals who are above the age of 60. (2) Within the United Kingdom's general populace, the incidence of major depressive disorder stands roughly around 10%.

Addressing this intricate condition effectively is indeed a daunting task, and the present gamut of treatment methods, which includes psychotherapy and medication, don't universally succeed in all patient scenarios, thereby underlining the imperative need for exploring alternative therapeutic strategies. (3,15)

One such exploratory alternative that has been increasingly gaining attention over recent years is the application of psilocybin, a naturally derived psychedelic substance found in particular types of mushrooms. Empirical research points to the potential of psilocybin as a therapeutic tool for a host of mental health maladies, depression included. In this in-depth review, our aim is to dissect the role of psilocybin as a depression treatment modality, investigating its operational mechanisms, the relevant clinical trials undertaken, and the potential risks and rewards that may accompany its usage.

Methods

We conducted a review in May 2023 searching for terms „depression”, „psilocybine”, „depression-resistant treatment”. We searched Pubmed and Google Scholar databases to find scientific papers addressing the treatment of depression with psilocybin based mainly on papers written between 2016 and 2023.

Mechanism of action:

Psilocybin's Metabolism and Neuropharmacology

When consumed, psilocybin is swiftly metabolized within the mucosal lining of the intestine, undergoing dephosphorylation catalyzed by specific enzymes like alkaline phosphatase and non-specific esterase. The outcome of this metabolic conversion is psilocin, the active form of psilocybin, which brings about its psychedelic effects (4).

The molecular architecture of psilocin bears similarity to that of serotonin, a crucial neurotransmitter implicated in mood regulation and various critical brain activities (5). This structural likeness grants psilocin the capacity to engage with certain serotonin receptors, with

the 5-HT_{2A} receptor being the primary one (6). Serving as an agonist to the 5-HT_{2A} receptor, psilocin forms a complex with the receptor and triggers its activation. The actuation of the 5-HT_{2A} receptor is widely considered as the pivotal mechanism catalyzing the psychedelic influence of psilocybin (7). This particular receptor is predominantly located in brain areas involved in perception, cognition, and mood modulation, including the prefrontal cortex (PFC) (8). In light of recent research findings, it is suggested that psilocybin could harbor therapeutic potential for treating depression by sparking alterations in neural activity across various brain areas, notably the default mode network (DMN), and by fostering neuroplasticity [8]. The DMN comprises a group of brain areas that are active during self-focused thought processes and ruminations, which are typically seen in depression. Studies indicate that psilocybin can reduce DMN activity, thereby lessening self-referential thought patterns and enhancing positive mood and emotional receptivity (9).

Furthermore, psilocybin has been demonstrated to stimulate the synthesis and release of brain-derived neurotrophic factor (BDNF), a protein that facilitates neuroplasticity, particularly within the prefrontal cortex (PFC). As a crucial brain region involved in emotional and cognitive regulation, the PFC is frequently linked to the pathophysiology of depression. Psilocybin is associated with an enhancement of neural interconnectivity within the PFC, a factor that could contribute to its antidepressant properties (10).

Results:

A pair of double-blind, placebo-controlled studies explored the impact of psilocybin on depressive and anxious symptoms within individuals diagnosed with life-threatening cancer. The initial study engaged 51 patients and documented noteworthy antidepressant and anxiolytic responses that endured for a span of up to 6 months, with 83% and 79% of patients achieving response benchmarks as per the Hamilton Anxiety Rating Scale (HAM-A) and Hamilton Depression Rating Scale, respectively (11). The subsequent study involved 29 patients and revealed that psilocybin catalyzed immediate and prolonged reduction of anxiety and depressive symptoms, with these effects persisting up until the concluding follow-up at 6.5 months. At this stage of follow-up, rates of response to antidepressant (Beck Depression Inventory, BDI) or anxiolytic treatments (Hospital Anxiety and Depression Scale, HAD-A) sustained high levels, falling within the 60-80% range (12).

In an individual randomized, double-blind, controlled trial, the effectiveness of psilocybin was juxtaposed with the routinely used antidepressant escitalopram for the treatment of depression. This study revealed that psilocybin facilitated improvements in depressive symptoms equivalent to those seen with escitalopram. While the distinction between the two treatment groups was not statistically significant, the investigators interpreted these findings as optimistic and supportive of additional exploration into the potential advantages of psilocybin-based interventions in depression management (13).

A distinct investigation scrutinized the enduring effects of therapy assisted by psilocybin in a cohort of 27 patients experiencing moderate to severe depression. The outcomes highlighted a substantial diminution in depression scores that lasted up to 12 months post-therapy, characterized by a 75% response rate and a 58% remission rate. The therapy demonstrated prolonged antidepressant effects and enhancements in mood, with no severe adverse events reported (14). A Phase 2 double-blind trial that included 233 participants evaluated the efficacy of singular doses of 25 mg, 10 mg, and 1 mg (control) of psilocybin, coupled with psychological support. As of the third week, the 25 mg dose manifested superior improvements in the severity of depression, anxiety, mood, and functioning compared to the 1 mg control, whereas the 10 mg dose resulted in smaller effects. These results suggest that psilocybin may have a potential role in ameliorating a range of patient-reported outcomes in treatment-resistant depression (15).

A particular study investigated the safety profile of concurrently administering psilocybin to healthy individuals within the most extensive randomized controlled trial thus far. In this Phase 1 study, healthy participants received either a singular dose of psilocybin (10 mg or 25 mg) or a placebo, aiming to evaluate its safety and impact on cognitive function and emotional processing. The findings indicated that psilocybin was generally well-tolerated, with no serious adverse events or marked adverse impacts on cognitive performance or emotional processing observed (16).

The potential therapeutic uses of psilocybin have been a growing area of interest recently, especially regarding its reported influence on enhancing neural adaptability and fostering the growth of new neurons. A study conducted on rats exhibited that the administration of psilocybin led to augmented neural adaptability and neurogenesis within the prefrontal cortex, a brain region tied to cognitive and emotional regulation. Furthermore, this study unveiled that psilocybin mitigates stress-related behavioral deficits observed in mice, with the structural changes brought about by psilocybin enduring for a minimum of one

month. Such dendritic reformation is accompanied by heightened excitatory neurotransmission (17). The likely utilization of psilocybin within the domains of neurosurgery and neurooncology is gaining prominence, given that patients in these categories often grapple with mood disorders. For example, up to 60% of individuals who have endured a stroke, intracranial hemorrhage, or head injury may also encounter depressive symptoms (18). The ability of psilocybin to augment neuroplasticity could potentially aid the revival of pathologically affected areas, thereby unveiling new therapeutic prospects for patients battling mood disorders stemming from neurological conditions.

Risks:

Psilocybin intake can introduce several risks and adverse effects. Unpredictable emotional reactions constitute one of the more prevalent negative responses to psilocybin use. The intensity and duration of these reactions can vary, potentially encompassing anxiety, paranoia, hallucinations, and disorientation. An unfavorable psychedelic experience, or "bad trip," can evoke distressing emotions, making the individual feel ensnared in a whirlwind of negative thoughts and emotions (19). Psilocybin may also exacerbate pre-existing mental health disorders: For those with a history of psychosis, schizophrenia, or other severe mental health conditions, psilocybin may intensify symptoms (20). One rat study also discovered that habitual psilocybin intake could lead to histopathological alterations in the myocardium, such as perivascular fibrosis, coronary vessel wall thickening, and subendocardial fibrosis (21). One of the negative effects observed was a minor influence on the QTc interval, which could be significant for patients with pre-existing cardiac conditions (22).

Psilocybin can interact with an array of medications and substances, resulting in modified experiences or adverse reactions. The full range of these interactions has not been entirely elucidated, necessitating more research to safeguard user safety and inform the guidelines for the use of psilocybin.

Conclusion:

The exploration of psilocybin as a possible therapeutic tool for depression has attracted substantial attention in recent times due to its prospective beneficial effects. Even though the field of research is still nascent, preliminary findings point to optimism,

showcasing enduring enhancements in mood and behavior, as well as a decline in depressive symptoms across both clinical and non-clinical groups. It's imperative to underscore that psilocybin is a powerful compound and its use should be restricted to suitable clinical oversight. The act of administering it should occur within controlled environments with proficient professionals present, ensuring the safety of patients. The unregulated consumption of this substance could prove perilous and potentially detrimental.

The call for additional research persists, aiming to more comprehensively comprehend the enduring implications of psilocybin on mental health and pinpoint any potential dangers linked to its usage. Furthermore, the legal standing of psilocybin remains a barrier to its broad acceptance as a therapeutic agent, highlighting the need for modifications in policy and shifts in societal perception. A vital facet requiring attention is the absence of standardized procedures for therapy assisted by psilocybin. Despite numerous investigations examining the application of psilocybin in depression treatment, no clear consensus has been reached on the optimal dosage, timing, or method of administration of the substance. The formulation of standardized directives and best practices for delivering psilocybin will be pivotal to fully harness its therapeutic potential and ensure consistently beneficial outcomes for patients.

To summarize, psilocybin presents a remarkable prospect as a novel approach to depression treatment. However, the fulfillment of its potential and integration into conventional mental health care demand continued investigation, the creation of standard therapeutic protocols, and alterations in its legal status.

Disclosure

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Our work did not involve direct human subject research or obtaining their consent for participation in the study

Data Availability Statement

As a review paper, our work does not present new data or analyses. Therefore, there are no specific datasets or data availability to report. The information and findings presented in this review are based on previously published studies, which can be accessed through their respective sources as cited in the reference section.

Conflict of Interest Statement

The authors declare that there are no significant conflicts of interest associated with this research work.

References

1. World Health Organization. Depression and Other Common Mental Disorders: Global Health Estimates. , [(accessed on 10 april 2023)]. 2017, www.who.int/publications/i/item/depression-global-health-estimates.
2. Depressive disorder (depression). *World Health Organization.*, [(accessed on 10 april 2023)] 2023, www.who.int/news-room/fact-sheets/detail/depression
3. Health National Institute of Mental. Depression. [(accessed on 10 april 2023)], 2019, www.nimh.nih.gov/health/topics/depression/index.shtml.
4. Passie T., Seifert, J., Schneider, U., & Emrich, H. M. The pharmacology of psilocybin. 2002, PMID: 14578010, DOI: 10.1080/1355621021000005937.
5. Nichols D. E. Hallucinogens. *Pharmacology & Therapeutics*. 2004, 101(2), 131-181. PMID: 14761703, DOI: 10.1016/j.pharmthera.2003.11.002.
6. Vollenweider F. X., & Kometer, M. The neurobiology of psychedelic drugs: implications for the treatment of mood disorders. *Nature Reviews Neuroscience*. 2010, 11(9), 642-651, PMID: 20717121, DOI: 10.1038/nrn2884.
7. Halberstadt A. L. Recent advances in the neuropsychopharmacology of serotonergic hallucinogens. *Behavioural Brain Research*. 2015, 277, 99-120, PMID: 25036425, PMCID: PMC4642895, DOI: 10.1016/j.bbr.2014.07.016.
8. Celada P., Puig, M. V., & Artigas, F. Serotonin modulation of cortical neurons and networks. *Frontiers in Integrative Neuroscience*. 2013, 7, 25, PMID: 23626526, PMCID: PMC3630391, DOI: 10.3389/fnint.2013.00025.
9. Carhart-Harris R. L., Roseman, L., Bolstridge, M., Demetriou, L., Pannekoek, J. N., Wall, M. B., ... & Leech, R. Psilocybin for treatment-resistant depression: fMRI-measured brain mechanisms. *Scientific Reports*. 2017, 7(1), 1-11, PMID: 29030624, PMCID: PMC5640601, DOI: 10.1038/s41598-017-13282-7.
10. Ly C., Greb, A. C., Cameron, L. P., Wong, J. M., Barragan, E. V., Wilson, P. C., ... & Olson, D. E. Psychedelics promote structural and functional neural plasticity. *Cell Reports*.

2018, 23(11), 3170-3182, PMID: 29898390, PMCID: PMC6082376, DOI: 10.1016/j.celrep.2018.05.022.

11. Robin L Carhart-Harris Mark Bolstridge, James Rucker, Camilla M J Day, David Erritzoe, Mendel Kaelen, Michael Bloomfield, James A Rickard, Ben Forbes, Amanda Feilding, David Taylor, Steve Pilling, Valerie H Curran, David J Nutt. Psilocybin with psychological support for treatment-resistant depression: an open-label feasibility study. *Lancet Psychiatry*. 2016, PMID: 27210031, DOI: 10.1016/S2215-0366(16)30065-7.

12. Stephen Ross Anthony Bossis, Jeffrey Guss, Gabrielle Agin-Liebes, Tara Malone, Barry Cohen , Sarah E Mennenga, Alexander Belser, Krystallia Kalliontzi, James Babb, Zhe Su, Patricia Corby , Brian L Schmidt. Rapid and sustained symptom reduction following psilocybin treatment for anxiety and depression in patients with life-threatening cancer: a randomized controlled trial. *Psychopharmacol*. 2016, PMID: 27909164, PMCID: PMC5367551, DOI: 10.1177/0269881116675512.

13. Robin Carhart-Harris Ph.D., Bruna Giribaldi, B.Sc., Rosalind Watts, D.Clin.Psy., Michelle Baker-Jones, B.A., Ashleigh Murphy-Beiner, M.Sc., Roberta Murphy, M.D., Jonny Martell, M.D., Allan Blemings, M.Sc., David Erritzoe, M.D., and David J. Nutt, M.D. Trial of Psilocybin versus Escitalopram for Depression. 2021, 384:1402-1411, PMID: 33852780, DOI: 10.1056/NEJMoa2032994.

14. Natalie Gukasyan Alan K Davis, Frederick S Barrett, Mary P Cosimano, Nathan D Sepeda, Matthew W Johnson, and Roland R Griffiths. Efficacy and safety of psilocybin-assisted treatment for major depressive disorder: Prospective 12-month follow-up. *J Psychopharmacol*. 2022 , 36(2): 151–158, PMID: 35166158, PMCID: PMC8864328, DOI: 10.1177/02698811211073759.

15. Guy M Goodwin Scott T Aaronson, Oscar Alvarez, Merve Atli, James C Bennett, Megan Croal, Charles DeBattista, Boadie W Dunlop, David Feifel, David J Hellerstein, Muhammad Ishrat Husain, John R Kelly, Molly R Lennard-Jones, Rasmus W Licht et al. Single-dose psilocybin for a treatment-resistant episode of major depression: Impact on patient-reported depression severity, anxiety, function, and quality of life. *Journal of Affective Disorders*. 2023 , 327:120-127, PMID: 36740140, DOI: 10.1016/j.jad.2023.01.108.

16. James J Rucker Lindsey Marwood, Riikka-Liisa J Ajantaival, Catherine Bird, Hans Eriksson, John Harrison, Molly Lennard-Jones, Sunil Mistry, Francesco Saldarini, Susan

Stansfield, Sara J Tai, Sam Williams, Neil Weston, Ekaterina Malievskaia, Allan H Young. The effects of psilocybin on cognitive and emotional functions in healthy participants: Results from a phase 1, randomised, placebo-controlled trial involving simultaneous psilocybin administration and preparation. *Journal of psychopharmacology*. 2022 , 36(1):114-125, PMID: 35090363, PMCID: PMC8801675, DOI: 10.1177/02698811211064720.

17. Ling-Xiao Shao Klara Liao, Iana Gregga, Pasza Davoudianin, Neil K. Savalia, Krystyna Delagarza, Alex C Kwan. Psilocybin induces rapid and persistent growth of dendritic spines in frontal cortex in vivo. *Neuron*. 2021 , 109(16):2535-2544.e4, PMID: 34228959, PMCID: PMC8376772, DOI: 10.1016/j.neuron.2021.06.008.

18. Kelly Daniel F. MD* i inni. Psychedelic-Assisted Therapy and Psychedelic Science: A Review and Perspective on Opportunities in Neurosurgery and Neuro-Oncology. 2023, 680-694, PMID: 36512813, PMCID: PMC9988324 (available on 2023-12-08), DOI: 10.1227/neu.0000000000002275.

19. Theresa M Carbonaro Matthew P Bradstreet, Frederick S Barrett, Katherine A MacLean, Robert Jesse, Matthew W Johnson, Roland R Griffiths. Survey study of challenging experiences after ingesting psilocybin mushrooms: Acute and enduring positive and negative consequences. *Journal of psychopharmacology*. 2016 , 30(12):1268-1278, PMID: 27578767, PMCID: PMC5551678, DOI: 10.1177/0269881116662634.

20. Nichols David E. Psychedelics. *Pharmacological reviews*. 2016 , 68(2): 264–355, PMID: 26841800, PMCID: PMC4813425, DOI: 10.1124/pr.115.011478.

21. Anna Machoy-Mokrzyńska Krzysztof Borowiak, Sławomir Majdanik, Paweł Łukaszczyk, Monika Białecka. Zmiany morfologiczne w mięśniu sercowym i naczyniach wieńcowych zaobserwowane po stosowaniu psylocyny w warunkach eksperymentalnych. *Problems of Applied Sciences*. 2017, Tom 6, s. 147 – 156, [(accessed on 10 april 2023) <https://bibliotekanauki.pl/articles/136060.pdf>

22. Elyes Dahmane Paul R Hutson, Jogarao V S Gobburu. Exposure-Response Analysis to Assess the Concentration-QTc Relationship of Psilocybin/Psilocin. *Clinical pharmacology in drug development*. 2021 , 10(1):78-85, PMID: 32250059, DOI: 10.1002/cpdd.796.