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Psilocybin as a new way for depression treatment

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Abstract:

Introduction: Mental disorders are common and still growing problem around the globe. Significantly decreasing quality of life, they are often source of true suffering for patients and their families leading to further health issues or even dramatic outcomes resulting in death. As public awareness rises, more and more people understand risks and tend to look for help as fast as possible. Currently available treatment methods are not always efficient enough to deal with more complex cases. Therefore it is important to look for new therapy options incrementing chances of fast and successful treatment.

Results: Studies showed that psilocybin is not only able to lower depression and anxiety scores in patients with major depressive disorders or with serious life-threatening conditions but also proved this effect to be long-lasting. At the same time, no or little adverse side effects were noticed.

Conclusions: Psilocybin is potentially a good method for depression treatment in some groups of patients. It should be considered if other, better known therapies show little or no effects.

Key words: psilocybin, depression

Introduction:

According to World Health Organization (WHO), about 970 million people around the globe suffered from any form of mental disorders in 2019. That was roughly one of every eight people living worldwide (1) . At the same time total disease burden measured in Disability-Adjusted Life Years (DALYs) for mental disorders alone was 125.31 million. This placed them on the 7th place of total disease burden share (2) . This clearly shows how widespread and common psychiatric diseases are. The two most common ones have not changed over the last decades as depression and anxiety still remain at the top. Even though other well-known disorders such as bipolar/eating disorder or schizophrenia affect much smaller groups of people, the number of patients can be still counted in millions (3). Not only do they suffer from certain disease but also often face with some sorts of stigmas impairing their normal everyday life in society. Worth to mention are also their families which have to cope with these problems as well. The burden comes with great distress, routine disruption and challenge of facing completely new obstacles in life (4).

Since depression and anxiety often come with huge stress, we cannot omit another huge group of patients dealing with other, non-psychiatric disorders, especially these considered lethal. Among over 21 000 oncologic patients analyzed in a study by Walker et al., 1599 were diagnosed with major depression. What is more, 73% of them did not receive any pharmacological support to cope with this situation (5). Another study by Tsaras et al. focused on a cohort of 152 breast cancer patients after different methods of treatment. Researches found that 38,2% of them were classified as depressed and 32,2% as anxious (6). Other severe and long-lasting conditions like autoimmune diseases were also described to be associated with higher prevalence of disorders mentioned above (7,8) . This is why treating proper treatment in psychiatry is so important.

Knowledge in medical sciences is improving and we have already been given a lot of clues about etiopathogenesis of various disorders. We have also significantly changed our approach to many of them both in terms of treatment and prognosis. However, despite years of research, many of our concepts have not developed beyond being only theories. Therefore, in many cases we still lack definitive conclusions of how disease develops and then impairs proper functioning. This leads to problematic topic of choosing the right procedures to help the patient as much as we can with little or none side effects. The history of psychiatry has some bright examples of controversial methods which sooner or later showed adverse outcomes leading to their complete ban. Since then, with further development of science,

better and safer therapies have been appearing with older ones being either improved or discontinued. As for today, patients choose from a wide range of different psychotherapy types, drugs or methods like electroconvulsive therapy. It is not uncommon to see them being combined to work complementary together (9,10) . However, even though the priority is to select the safest treatment options, sometimes it may not be enough forcing the usage of less specific medicines with stronger side effects. That may be associated with achieving a desired response at a cost that is hard to accept for the patient. To avoid such issues, researchers still look for new alternatives. One of the possibilities can be natural compounds found in organisms humanity has known for thousands of years. Substances like mescaline found in different species of cacti or psilocybin derived from mushrooms gain more and more attention due to their properties and possibilities (11).

The aim of this study was to assess available literature in order to determine the possible usage of psilocybin in treatment of psychiatric disorders.

Methods:

Pubmed, Scopus and Google Scholar databases were searched using keywords “psilocybin”, “psychiatric disorders”, “depression”. The articles had to be published between 2016 and 2024 to be asses.

Description of knowledge:

Psilocybin (*O*-phosphoryl-4-hydroxy-*N,N*-dimethyltryptamine, 4-PO-Psilocin or 4-PO-HO-DMT) is an organic compound classified as alkaloid found in various species of Basidiomycota mushrooms, mostly Psilocybe genus, commonly called “hallucinogenic” or “magic” mushrooms. It is described as a prodrug that in the course of dephosphorylation by alkaline phosphatase and nonspecific esterase in mucosa turns into its pharmacologically active form called psilocin (12). This compound, due to its structural similarity with serotonin, acts as an agonist for serotonin (5-hydroxytryptamine or 5-HT) receptors, mainly 5-HT_{2A} (13). Interestingly, it also has moderate affinity to non-5-HT receptors such as dopamine D3 receptors and weak affinity to imidazoline 1 receptors (14) . Macroscopic effects of this substance were able to be described thanks to magnetic resonance imaging studies. According to them, psilocybin reduces brain activity in its parts connected with major depression disorders. Decreased cerebral blood flow and venous oxygenation in ventral medial prefrontal cortex, thalamus, anterior and posterior cingulate cortices were found right after intravenous

infusion (15) . Nevertheless, the effects of psilocybin are widely varied and affect both physical and mental spheres of the body. In physical way, patients mostly report changes in heart rate, pupil dilation, changes in blood pressure and stretch reflex, nausea, tremor and dysmetria (16). Much more interesting and also important is what happens with their mind, as psilocybin has been known for its hallucinogenic properties for thousands of years. While small amounts only tend to cause dizziness and emphasize individual's mood, doses above 15 mg of oral intake already lead to psychedelic effects. They are described as changes in perception (illusions, hallucinations, synesthesiae etc.), changes in body perception and self-perception, derealization/depersonalization, impaired perception of time and space, impaired attention and thought content disorders. Users were also likely to experience mood swings, which can vary from ecstatic to anxiety (12). Psilocybin may also induce strong mystical and spiritual experiences what is still being used in some indigenous cultures. Safety of this substance, just like in other drugs, is deeply connected with proper set and setting. What is more, studies have not shown correlation with psilocybin intake and triggering psychotic episodes or acute symptoms. The risk of addiction is very low as well (17). Its toxicity is hard to estimate because of lethal dose being much higher than the psychoactive one. It is estimated to be around 6 grams, about 1000 times higher than the effective dose (18) . However, due to the possibility of bad trip occurrence and extensive range of effects with high individual variability, it is difficult to predict how safe it is overall.

Due to their properties, psilocybin mushrooms are now illegal in most states around the world. First research on their potential usage in psychiatry have been already carried on in 1960s by Timothy Leary. The outcomes were promising but public concerns and strict laws suspended further analysis (19,20) . They came back at the beginning of 2000s once again showing potential. In the last few years more and more researchers focus on them in search of new, better ways of treating patients. Unfortunately, while there are many papers about depression, databases still lack information about other most frequent psychiatric disorders. This is why we focused specifically on depression in this review.

In 2016, a team led by Carhart-Harris tried psilocybin on a group of twelve patients with mostly unipolar, severe and treatment-resistant major depression. They obtained it in two oral doses (10mg and 25mg) given them 7 days apart in supportive setting, with psychological aid before, during and after each session. Their response was assessed with QIDS-SR16 (16-item Quick Inventory of Depressive Symptoms). Compared to baseline, scores were lower both after a week (mean QIDS difference −11·8, 95% CI −9·15 to −14·35) and 3 months

(−9·2, 95% CI −5·69 to −12·71) after high-dose treatment. Improvements in anxiety and anhedonia were noted as well (21) . Two years later, in 2018, these researchers carried out almost identical study on twenty patients with the same disorders. Doses given to participants were the same as in the previous study. Compared to baseline, QIDS-SR16 scores were reduced in all of six post-treatment time points. Out of 19 patients who completed all of them, every single participant showed some reduction of depression severity at week 1 with the best results at week 5. They did not report any severe side effects apart from 1-2 day headaches or nausea without vomiting (22). Treatment-resistant depression was also point of interest of two studies carried out by Guy M. Goodwin with coworkers in 2022 and 2023. The first one was phase 2 double-blind trial with the total of 233 participants randomly assigned to receive single dose of 25mg (79 people), 10mg (75 people) or 1 mg (control group of 79 people). They were also given proper psychological support. Montgomery–Åsberg Depression Rating Scale (MADRS; range, 0 to 60, with higher scores indicating more severe depression) was used to evaluate treatment progression. The mean score of MADRS was 32-33 in each group. At week 3, mean changes were -12.0 in 25mg, -7.9 in 10mg and -5.4 in 1mg. An important limitation in these findings is that 77% of participants suffered from adverse effects. What is more, suicidal ideation/behavior or self-injury occurred in all of three groups (23). The second trial was a phase 2, exploratory, international, fixed-dose, open-label study evaluating psilocybin usage as an addition to selective serotonin reuptake inhibitors. Participants were adults taking single SSRI (citalopram, escitalopram, fluoxetine, paroxetine, sertraline, vilazodone, and vortioxetine were allowed) and not experiencing any major comorbid psychiatric disorder or suicide risk. They were given single dose of 25mg psilocybin along with proper psychological support. Mean MADRS score in the group of 19 participants who finished the trial was 31,7 at the beginning and at week 3 its mean change was -14,9. This time only 63,2% of participants had treatment-emergent adverse effects most of which were mild and disappeared at the day of onset (24). The amount of 25 mg was also used by Charles L. Raison et al. in their randomized, placebo-controlled trial on 104 adults with MADRS score equal or greater than 28 and with equal or less than 30% improvement during 7 to 35 days of prior psychiatric treatment. Fifty of them received psilocybin, while the remaining 53 received niacin. At day 43, a much more significant decrease in MADRS score was observed in psilocybin group with mean difference of -12,3. What is more, this group was associated with bigger chance of sustained response, but not with remission. It is worth noting however that 88% of participants in psilocybin group and 61% in niacin group reported at least one

adverse effect through day 43 (25). Positive effects of psilocybin-assisted therapy were also noticed in 2020 in a study by Davis et al. Twenty-seven adults aged 21-75 with major depressive disorder were randomized to immediate treatment condition group or to delayed treatment condition group (waiting list). Doses were given two times again with 20mg/70kg at session 1 and 30mg/70kg at session 2. In the overall sample, 17 (71%) at week 1 and 17 (71%) at week 4 had a clinically significant response and 14 (58%) and 13 (54%) respectively were in remission (26).

Research groups focused on patients with life-threatening cancers as well. In a study from 2016 carried out by Griffiths et al. all of 51 patients were diagnosed with neoplasms and symptoms of depression or anxiety. Scientists designed randomized double-blind trial with one group given very low, placebo-like doses of 1-3mg/70kg and the second group given high doses of 22 or 30 mg/70kg. Drugs were administered in counterbalanced sequence with 5 weeks between session and follow-up of 6 months. Once again, group treated with higher doses reported significant decrease of depression measures and these changes sustained at 6-month follow-up (27). Patients with cancers were also assessed in a double-blind, placebo-controlled, crossover trial by Ross et al. from 2016. Twenty-nine patients with carcinomas with related depression and anxiety were enrolled and then given single-dose psilocybin (0,3mg/kg) or niacin. Pharmacotherapy was accompanied psychotherapy. Research showed immediate, substantial and sustained improvement both in anxiety and depression. At 6,5-month follow-up, 60-80% of patients continued with progress mentioned above (28). In 2023 Agrawal et al. conducted phase 2, open label trial focusing curable and non-curable oncological patients with major depression disorders. Participants were given a single 25mg dose of psilocybin. Out of 30 patients enrolled, 80% presented a sustained response and 50% showed full remission of depressive symptoms at week one. This outcome persisted at week 8 (29).

To show comparison between psilocybin and drugs that are commonly in use nowadays, in 2021 Carhart-Harris et al. carried out another study in which they analyzed how would it contrast with escitalopram, a selective serotonin reuptake inhibitor (SSRI). A double-blind, randomized, controlled trial involving 59 patients with severe of moderate depression was carried out over a time of 6 weeks. One group received two separate oral 25 mg doses of psilocybin 3 weeks apart with 6 weeks of daily placebo and another got two separate oral 1 mg psilocybin doses 3 weeks apart with 6 weeks of daily oral escitalopram. The mean scores of QIDS-SR16 at baseline were 14,5 in the first and 16,4 in the second group. The mean (±SE)

changes to week 6 were -8.0±1.0 for psilocybin and -6.0±1.0 for escitalopram. For the first group, response occurred in 70% of the patients and for the second in 48%. Remission occurred in 57% and 28% respectively. However, even though this study showed difference between these two therapies it wasn't significant enough to favor psilocybin over more traditional antidepressants (30).

An important aspect of long-lasting effects of psilocybin curation was described by Gukasyan et al. in 2022. Researchers examined its efficacy and safety over 12-month-long study on 21 patients aged 21 to 75 with moderate to severe unipolar depression (GRID-Hamilton Depression Rating Scale [GRID-HAMD] $\geqslant$ 17). Treatment response ($\geqslant$50% reduction in GRID-HAMD score from baseline) and remission were observed in 75% and 58% of participants respectively. Interestingly this study reported no adverse effects connected with psilocybin (31).

Conclusions:

Recent years brought an increased interest in the potential of psilocybin in psychiatry. Its relative safety, small risk of addiction, natural origin and costs of production make it a great alternative for patients struggling with resistance to more traditional therapies. Studies show that with proper set and setting it can help them with depression and anxiety and in many cases this effect is long-lasting. However, some papers lack controlled groups or have serious limitations and there are still too few papers focusing on other psychiatric disorders. Therefore, to fully understand possibilities psilocybin gives, more research is still needed.

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