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Psilocybin - new remedy for patients with psychiatric disorders? Critical analysis of the current state of knowledge

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Summary:

Introduction and purpose:

Nowadays, when mental disorders are considered by the World Health Organisation as a global burden, the potential usage of psychedelic drugs as supportive therapy is gaining more attention worldwide. The aim of this paper is to summarize the usefulness of psilocybin - representative of psychedelics - in psychiatric venues. In this review we describe its

properties, efficacy and adverse events in treating depression, trauma and obsessive-compulsive disorders.

Brief description of the state of knowledge:
Psilocybin demonstrates a safety profile which does not differ from standard drugs used in therapies of psychiatric disorders. Positive results of its administration were noticed on different psychiatric scales and are considered as clinically meaningful. With depression being the most common mental disease and growing demand for new remedies, most of the conducted research is concentrated on this subject, but there is also some evidence of its purpose in the treatment of trauma and obsessive-compulsive disorders.
Conclusions:

Psilocybin merits further research as foregoing results of conducted studies are pointing to its efficacy. Psychedelic-assisted therapies may create noteworthy opportunities to current matter in the standard treatment of psychiatric disorders and there is a possibility that in the future in some cases they will be considered as the first line treatment. Nevertheless, still more data is needed to determine its placement in the treatments.

Key words: psilocybin; depression; mental disorders; psychedelics; health

1. Introduction

Psilocybin is a compound found in mushrooms widely known for its hallucinogenic properties. Due to these effects, its potentially therapeutic actions remained unexplored for many years. However, in the last decade, a breakthrough occurred, and research into its applications in treating, among other conditions, treatment-resistant depression, began. Despite the general knowledge that psilocybin is a non-specific agonist of serotonin receptors, its precise effects on the human brain are still unknown [1]. It is hypothesized that its potential results in patients with depression may occur through mechanisms such as

interactions with neuroreceptors and an increase in blood flow to the amygdala and prefrontal cortex [2].

2.1 General guidelines for depression treatment

General agreement exists for major depression treatment guidelines and includes individualized treatment plans, making the patient aware of the possibility of long-term treatment and treating until disease remission. The treatment of depression involves both antidepressant medication and psychotherapy, which has positive, but small effects [3]. As first-line treatment for mild depression psychotherapy and symptom monitoring are preferred, while pharmacotherapy should be considered in cases of insufficient improvement. For moderate depression psychotherapy, as well as pharmacotherapy or both, might be useful [4]. In severe depression treatment, the combination of antidepressant and antipsychotic drugs, electroconvulsive therapy or the combination of an antidepressant and psychotherapy may be required [5].

Several different types of psychotherapy such as cognitive behavior therapy (CBT), behavioral activation therapy (BAT), interpersonal psychotherapy (IPT), problem-solving therapy and non-directive counseling have been developed. Data has not shown significant differences in efficiency between these different types of psychotherapy, therefore the patient's situation should be taken into account in choosing suitable therapy [3]. Meanwhile studies indicate that psychotherapy is preferred by patients over pharmacological treatment [6,7]. It might be related to severity of depression - patients with severe depression are more likely to use drugs [8]. It has been also noticed that younger patients reported stronger preferences for psychotherapy than older patients [6].

Antidepressant medication has been the current standard of treatment for depression, although the present findings question their efficacy in milder forms of depression and indicate that effects can depend on the severity of symptoms. Fournier et al. reported that the size of antidepressant medication’s effect is variable according to the symptoms severity of depression. Effects were smaller in cases of mild depression but greater in moderate and severe depression [9].

The most common, first-line antidepressant medications include selective serotonin-reuptake inhibitors (SSRIs), serotonin-norepi-nephrine-reuptake inhibitors (SNRIs), bupropion and mirtazapine. Then FDA approved four more drugs as depression treatment options: desvenlafaxine, vilazodone, vortioxetine and levomilnacipran. In case of these drugs

inefficiency older classes of antidepressants including tricyclic antidepressants and monoamine oxidase can be used, but they are not common because of their greater risk profile in comparison to the newer agents [4]. The work conducted by Cipriani et al. aimed to do a systematic review and network meta-analysis to compare different antidepressants. The results revealed agomelatine, amitriptyline, escitalopram, mirtazapine, paroxetine, venlafaxine and vortioxetine as more effective than other antidepressants, whereas fluoxetine, fluvoxamine, reboxetine and trazodone were among the least efficacious drugs. In head-to-head trials larger differences in the efficacy and acceptability of individual antidepressants were observed. Agomelatine, citalopram, escitalopram, fluoxetine, sertraline and vortioxetine were found to be better tolerated than other antidepressants [10].

A precise choice of medication is guided by adverse-effect profiles as well as by the patient's medical history including coexisting psychiatric disorders, clinical picture of depression and treatment history. The selection also should take into account the patient's history of medication response, side effects presented during therapy, personal preferences, drugs' prices and their acceptability [11]. Treatment usually begins at a low dosage and effects are assessed after an appropriate period of follow up. Early improvement may be noticed in two weeks, but full relief of symptoms may not be observed even for 8 to 12 weeks [4]. After achieving remission, treatment should be continued for at least 6 months, which decreases the risk of further relapse [12].

Some studies revealed also that some dietary supplements might bring benefits for patients with depressed mood. In this light diet should be based on the polyunsaturated fatty acids (PUFAs), combining eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), vitamin D and probiotics. Hence, they are proposed as adjective therapies for depression treatment. It is consistent with the assumption, in which inflammation and dysfunction of the gut–brain axis are pathogenetic elements of depression [13]. Moreover, some specific groups of foods such as fish, nuts, seeds, fruits, vegetables, coffee, tea and fermented products and dietary supplements including S-adenosylmethionine, acetyl carnitine, creatine, amino acids are currently being investigated for their usefulness in depression therapy. Also some dietary strategies such as Mediterranean diet, low-carbohydrate diet and plant-based diet (vegetarianism and veganism) seem to support the prevention and treatment of depression. What is highlighted, the type of dietary strategy is less important than the healthy dietary pattern, which includes a wide variety of food and nutrients [14].

Another therapeutic strategy known as phytopharmacotherapy might be useful especially in treating mild or moderate depression. It is based on active compounds in plants such as St.

John's wort, saffron crocus, lemon balm and lavender or less known in European ethnopharmacology, roseroot, ginkgo, Korean ginseng, borage, brahmi, mimosa tree and magnolia bark and their antidepressant activity with similar mechanisms to those observed in synthetic antidepressants [15].

Advanced non-pharmacological techniques, such as repetitive transcranial magnetic stimulation (rTMS) or electroconvulsive therapy (ECT), might be also required in severe depression treatment. Both of them are effective with ECT superior compared to rTMS [16].

Only the minority of patients with depression are referred to mental health services. Most of them are treated in primary care [17]. It should be noticed, that psychiatric consultation is obligatory for patients with severe depression and in case of patients presenting psychotic symptoms or suicidal thoughts and behaviors [4].

2.2 Possibilities of using psilocybin and its effectiveness in the treatment of depressive disorders and trauma

Several studies were conducted in order to assess the effectiveness of psilocybin in the treatment of depression.

In a study in which psilocybin was administered to the patients with advanced-stage cancer and anxiety the results showed physiological and psychological improvement. Those findings were measured by using the State-Trait Anxiety Inventory at 1 and 3 months after the treatment and The Beck Depression Inventory at 6 months of the treatment. All patients had two sessions of therapy: one of them was the 0.2 mg/kg dose of psilocybin and the second one was 250 mg of niacin. During the study and in the follow-up no serious adverse events were reported [18].

Another randomized study similarly conducted on patients diagnosed with cancer and signs of depression and anxiety weighted the impact of different doses of psilocybin on 51 participants. One group received a low dose of the drug (1 or 3 mg/70 kg) and the second one the high dose (22 or 30 mg/70 kg) in two doses within a 5 week interval. The results were evaluated by using the GRID-Hamilton Depression Rating Scale and the Structured Interview Guide for the Hamilton Anxiety Rating Scale. Both groups noted clinically meaningful responses, although a group treated with the higher dose of psilocybin showed greater progress. During the 6-months follow-up obtained results were maintained and about 80% of the participants persisted in improving their mood and attitude. As in the previous paper no serious adverse events were observed [19].

Another study with 29 contributors aimed to compare the effects of psilocybin and niacin on patients diagnosed with depression and anxiety related to cancer diagnosis. Both groups underwent psychotherapy during the treatment. In turn, the first group manifested advancement in their psychological condition. In addition psilocybin was also established as an enhancer to other anxiolytic and antidepressant drugs [20].

In 2021 Carhart- Harris et al. conducted a trial that compared the effects of psilocybin with escitalopram - a well known anti-depression drug. There were no clinically meaningful differences between the two groups in the Quick Inventory of Depressive Symptomatology–Self-Report. Although, during the trial group with psilocybin showed better improvement in secondary outcomes - three clinically validated depression scales while the frequency of adverse effects were similar in both groups [21].

Nevertheless, further Bayesian reanalysis concluded that even though psilocybin seemingly showed better results when the interpretation of the results is more nuanced and precise they can not be considered as clinically meaningful and thereupon psilocybin should not be marked as superior to escitalopram [22].

Metaanalysis of studies that were made on humans highlighted that response to psilocybin is related with applied dose. Authors also emphasized that the doses should be fitted individually according to the patient's age and previous experiences with psychedelics as it is a big factor in efficaciousness of the therapy [23].

Psilocybin seems also to be applicable in the therapy of trauma. In a study conducted by Healy et al. on 166 participants, patients that admitted to use psychedelics noted lower complex trauma manifestations comparatively to those not using psychedelics with similar history in their past - all participants experienced child maltreatment in their childhood years. Those conclusions were made by analyzing the questionnaires such as Childhood Trauma Questionnaire and International Trauma Questionnaire. In this study patients were using different psychedelics, but psilocybin was the most frequent one (67,3% of all) [24].

Another study confirming the psilocybin therapeutic utility was the one conducted by Khan et al. In this paper authors evaluated the role of psilocybin in trauma-related disorders by using the available literature - although their conclusions were promising, it was noted that further studies are needed as the available data is still insufficient [25].

Anderson et al. conducted an open label pilot study in which eighteen men diagnosed with AIDS underwent psychotherapy in tandem with psilocybin supplementation. During the study there were not reported serious adverse reactions. The results showed clinically meaningful improvement in patients' behavior that was continued during the three months

follow-up. Although in this follow- up three serious adverse events were observed: stimulant-induced psychosis, suicide attempt and cholecystis. All of them were established as not correlated with the use of psilocybin. During the therapy patients noted mostly hypertension, nausea, headache, paranoia, restlessness, ataxia. Those adverse effects are not perceived as serious, but are considered to be linked with the use of psilocybin [26].

2.3 Possibilities of using psilocybin and its effectiveness in the treatment of drug-resistant depression

Treatment-resistant depression (TRD) is a term without a universally accepted definition worldwide. Typically, the term TRD is used to refer to depression in which standard treatment with two medications at appropriate doses and duration has not yielded clinical improvement [27]. It is estimated that in the USA, the issue of TRD affects 2.8 million (30.9%) individuals with major depressive disorder (MDD) [28]. As a result, providing appropriate treatment for individuals suffering from TRD poses a challenge for modern medicine and improving treatment efficacy is being pursued through the investigation of drugs that are intensely studied for their effectiveness. Among such drugs are ketamine and psilocybin [29,30].

In recent years, there have been numerous reports on the use of psilocybin in the treatment of treatment-resistant depression (TRD). In 2022, Guy M. Goodwin et al. published scientific work on the impact of psilocybin in treating TRD. This was a phase 2 double-blind trial and patients participating in this clinical study were administered a single dose of psilocybin (25 mg, 10 mg, 1 mg). A total of 233 individuals were involved in the study. The effectiveness of the treatment was assessed using the MADRS scale, which showed improvement in patients receiving 25 mg compared to those receiving 1 mg. After 3 weeks, a reduction in the severity of depression, as measured by the MADRS scale, was observed in the 25 mg group by 12 points. There was no significant statistical difference observed between the 10 mg and 1 mg groups. The highest doses were associated with the most common adverse events, which included headache, nausea, and dizziness. However, this study did not employ a comparative control group of patients treated with conventional antidepressant medications [31].

Lea J Mertens et al. described changes in brain connectivity after treating TRD with 25 mg of psilocybin and demonstrated that emotional responses in these patients improved [32]. In a study published in 2023, the impact of a single 25 mg dose on patients treated for TRD who were concurrently taking SSRI medication was examined. The average duration of SSRI

intake was 14.68 months. The study included 24 participants, of whom 19 completed the study. Significant improvement was shown on the MADRS scale. In 8 individuals (42.1% participants), the MADRS score decreased by >50% after 3 weeks, indicating reduced depression symptoms. Notably, no participants experienced clinical worsening after 3 weeks. Psilocybin administration resulted in adverse effects in 12 patients. Most of these effects occurred and resolved within 1 day after psilocybin intake [33].

The optimal dosing of psilocybin is still undetermined. It remains unclear whether a single large dose or multiple smaller doses are more effective. In 2017, the impact of two doses of psilocybin (10 mg and 25 mg) administered 7 days apart to TRD patients was studied. Additionally, patients received psychological support. The patients were then observed for 6 months. The treatment was well-tolerated and statistically improved their clinical condition. While the results of this study were promising, it is uncertain whether psilocybin administration or psychological support had a greater impact on their health. However, the fact that no patient sought conventional treatment for 5 weeks might suggest that psilocybin administration played a crucial role [34].

Despite ongoing research, the optimal dosage and treatment duration are still uncertain. Although the results of studies show promise, they have been conducted on a limited number of participants, and substantial randomized trials and meta-analyses are required.

2.4 Possibilities of using psilocybin and its effectiveness in the treatment of obsessive-compulsive disorder

Psilocybin may be also useful in treating obsessive-compulsive disorder (OCD), which is a chronic disorder characterized by unwanted and distressing thoughts (obsessions) and repetitive behaviors that the patient feels driven to reveal (compulsions).

The first clinical trial conducted by Moreno et al. in 2006 involved 9 patients with OCD who were administered different doses of psilocybin. This strategy resulted in reductions in OCD symptoms, although no clear dose effect was seen. The trial also revealed that psilocybin might be safely used, because there were no severe adverse events observed [35].

Recently, Ching et al. presented the protocol for a randomized, double-blind, placebo controlled trial, which sought to examine safety, tolerability and clinical and neural effects of single-dose psilocybin intake in OCD treatment. 30 adult patients are enrolling and will receive a single dose of oral psilocybin (0.25 mg/kg) or active placebo-control agent (250 mg of niacin). The effects will be assessed by the Acute Yale-Brown Obsessive-Compulsive

Scale and Visual Analog Scale ratings in the primary endpoint of 48 h post-dosing. Also resting state neuroimaging data will be stored both at baseline and primary endpoint. It is expected that psilocybin might lead to a rapid and substantial reduction in OCD symptoms, hence it would be able to treat refractory OCD [36]. According to clinicaltrial.gov (last update mid-July 2023) the trial is still in the recruiting phase.

There are also 3 case studies available which presented psilocybin's effect on OCD symptoms. The first one reported reduction in OCD symptoms in a 38-years old man after psilocybin administration, but it was accompanied by unpleasant and anxiety-provoking feeling (later reduced), along with the feeling of dissociation (lasted till 4 hours) [37]. Also Moreno et al. described improvement on OCD symptoms after psilocybin ingestion in a 34-years old man. Side effects such as dizziness, nausea, occasional vomiting and feeling of dissociation briefly after intake was noticed [38]. The last case study of a 30-years old man presented 63% reduction in symptoms of OCD over a month assessed by the Yale-Brown Obsessive-Compulsive Scale. Likewise in previous case studies dissociation after an hour of intake was also reported [39].

3. Conclusions

Currently depression is the fourth most often disease and one of the most often reason of committing the suicides. Predictions for the future are even more oppressive as WHO states by 2030 depressive disorders will be the most common disease in the world. Antidepressant treatments or psychotherapy are available, but a large proportion of patients do not reach a successful response. Hence, new therapeutic options are being examined. This paper presented updated data from observational and trial data, which assessed psilocybin as a new therapeutic option for some psychiatric disorders such as treatment-resistant depression, depressive disorders, trauma and even obsessive compulsive disorder. Foregoing results are promising and indicate that psilocybin might be especially useful for these unresponsive disorders. Therefore, psilocybin merits further research as new possibilities for treatment of psychiatric disorders are needed.

Author Contributions:

Conceptualization, K.W. and S.T.; methodology K.W; software K.W.; check, M.W. K.W. and S.T.,; formal analysis, K.W.; investigation, M.W.; resources, S.T; data curation, S.T.;

writing - rough preparation, K.W. M.W. and S.T.; writing - review and editing, K.W. S.T and M.W.; visualization, K.W.; supervision, K.W.; project administration, M.W.

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