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The use of psilocybin in the treatment of psychiatric disorders – review

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Abstract

Introduction: The word "psychedelic" derives from the Greek language and can be loosely translated as "mind manifesting" which is to convey that these substances allow the mind to unleash its hidden potential. Psilocybin is considered to be a "classic psychedelic" and is most commonly found in the form of so-called "magic mushrooms". Due to its unique properties psilocybin has been used during religious ceremonies and rituals for centuries and more recently also explored in a medical context. Nowadays many studies are being carried out to prove the efficacy of its use in the treatment of various psychiatric disorders.

Aim of study: Review of the current knowledge on the subject of psilocybin applied in the treatment of psychiatric disorders, such as major depressive disorder, treatment-resistant depression and addiction.

Methods and materials: A review of chosen literature was carried out in the PubMed database and Google Scholar using the following phrases: psilocybin, psychedelics, psychedelic-assisted therapy, major depressive disorder, addiction.

Results: Recent studies suggest that psilocybin may be an effective form of treatment for cancer-related psychiatric distress, treatment-resistant depression and addiction. There are some reports of psilocybin being useful when treating obsessive-compulsive disorder and cluster headaches.

Conclusions: More large-scale, randomized, placebo-controlled studies are required to prove these promising findings. Psychological support is crucial during the treatment with psilocybin.

Keywords: psilocybin, psychedelics, psychedelic-assisted therapy, major depressive disorder, addiction

Introduction

The word “psychedelic” derives from the Greek language and can be broken down into “psyche” (the mind or soul) and “delos” (to show) and was first used by Humphry Osmond, a psychiatrist, in 1956.[1]

Psilocybin, a classic psychedelic, has rare psychoactive properties which found its use in spiritual ceremonies throughout the centuries but more recently have also been explored for its potential application in medicine. Due to their connotation to the “hippie” movement psychedelics were stigmatized. As a result, psilocybin was classified as a Schedule I substance in the seventies, meaning “it has a high potential for abuse, no currently accepted medical use in treatment in the United States, and a lack of accepted safety for use under medical supervision” [2] which stalled the investigation of medical use of this substance. It also led to further deterioration of the public opinion on psilocybin and psychedelics in general. The subject resurfaced at the beginning of the 21st century when psilocybin was used in a pilot study at the University of California, Los Angeles in the treatment of patients with advanced stages of cancer. Its findings were very promising and allowed subsequent researchers to explore the topic of psychedelics and their clinical use in this and other applications further.

Psilocybin is a naturally occurring alkaloid, most commonly found in the form of various species of mushrooms. It cannot cross the blood-brain barrier itself however its active metabolite, psilocin, is more lipophilic and therefore more active. The effect-producing metabolite has a structure very similar to that of a serotonin molecule and is a 5HT-2A agonist and because of that has been eagerly explored by medical professionals, especially those specializing in psychiatry.

This review will outline the potential use of psilocybin in chosen psychiatric disorders. It will also touch on its safety profile and potential side effects.

Aim of study

Review of the current knowledge on the subject of psilocybin applied in the treatment of various psychiatric disorders, such as major depressive disorder, treatment-resistant depression and addiction.

Methods and materials

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Pharmacokinetics

Psilocybin, a water-soluble substance, is not an active compound itself. Its metabolite, psilocin, which is lipophilic crosses the brain-blood barrier and produces neurological effects[3,4]. In most studies subjects who are being administered psilocybin are in the state of fasting, consuming only water, which usually lasts between 2 to 4 hours and therefore the data on pharmacokinetics is true for these conditions. When ingested orally, the bioavailability of the psychedelic reaches 50%.

The onset of action is between 20 to 40 minutes and peak subjective effects typically occur within 60 to 90 minutes post administration, with an active duration amounting to 4 to 6 hours[5]. Most of the patients eliminate the active compound from their system 8 hours after the intake of psilocybin

but complete excretion may take up to 24 hours.

Dosing

Various doses are applied in different studies but generally they can be divided into standard, high and supra-therapeutic, being 25, 35 and 50-60 mg respectively [6,7,8,9]. This concerns pure psilocybin either in the form of an extracted isolate or a synthetic substance. It is generally considered that the “magic mushrooms” contain approximately 1% of psilocybin per 1 gram of dried mushroom weight, thus their doses are about 100 times higher than those mentioned above. However, there is a big variability when it comes to the content of the pure substance in different species of mushrooms. It varies between 0,5 and 2%[10,11] which should result in great caution while using this form of the psychedelic and assessing the effects it produces.

Therapeutic uses

There is strong evidence supporting the use of psilocybin in cancer-related depression[12,13,14], cancer-related anxiety[12,13,14] and treatment-resistant depression[15,16,17]. There is moderate-level

evidence for the use of this compound in the treatment of alcohol use disorder[18,19] and tobacco addiction[20]. Some open-label trials and case reports suggest utility of the psychedelic in obsessive compulsive disorder[21], cluster headaches[22] and demoralization with AIDS[23]. Due to its unique properties the researchers are curious about other potential applications of the drug and therefore studies considering its efficacy in anorexia, bipolar disorder and chronic pain are currently being carried out.

In a 2016 randomized double-blind trial R.R.Griffiths and coworkers investigated the administration of very low (placebo-like) dose (1 or 3mg/70kg) vs high dose (22 or 30mg/70kg) of psilocybin in 51 cancer patients with symptoms of anxiety and/or depression. The group receiving high doses reported decreases of depressed mood, anxiety and death anxiety while their self-rated quality of life, life meaning and optimism significantly improved. About 80% of the patients continued to experience these positive changes 6 months after the therapeutic psilocybin session, observing increased well-being and life satisfaction.[12]

C.S. Grob and coworkers conducted an investigation in 12 patients with advanced-stage cancer and anxiety using moderate doses of psilocybin (0,2/kg). According to the questionnaires carried out 1 and 3 months following the treatment patients reported significant reduction in anxiety. They also experienced mood enhancement at 6 months post the administration of the substance.[13]

Anxiolytic and antidepressant effects of psilocybin were observed in a double-blind, placebo-controlled trial where 29 patients with cancer-related anxiety were administered a single dose (0,3/kg) of psilocybin. Improvement in anxiety and depression with increased quality of life were observed immediately after treatment as well as at the 6,5-month follow-up.[14]

The use of psilocybin has been proven effective in the treatment of major depressive disorder (MDD) and treatment-resistant depression. In an open-label trial 26 patients diagnosed with treatment-resistant depression received two oral doses of psilocybin (10 and 25 mg, 7 days apart) in a supportive setting. Significant reduction in depressive symptoms was observed during the first 5 weeks following the therapeutic intervention. In 14 patients this was also true at 3 and 6 months post psilocybin ingestion and they did not seek conventional treatment for their psychiatric disorders.[15]

A placebo-controlled, double-blind, randomized clinical trial carried out in Zurich between 2019 and 2021 involving 52 patients with MDD proved the efficacy of single-dose psilocybin-assisted

therapy. Its participants reported a significant decrease in symptom severity which was far greater than that of the placebo group. Two weeks after the therapeutic session 14/26 (54%) participants met the remission criteria in the psilocybin condition.[16]

Comparison of psilocybin to escitalopram, a classic selective serotonin reuptake inhibitor, was done by R.Carhart-Harris and his team in a phase 2, double-blind, randomized, controlled trial involving 59 patients with long-standing, moderate-to-severe major depressive disorder. The results were similar in both groups of patients suggesting antidepressive effects of psilocybin resembling those of classic antidepressants.[17]

A single-group proof-of-concept study on 10 volunteers with DSM-IV alcohol dependance consisted in oral administration of psilocybin during one or two supervised sessions in combination with positive enhancement therapy. Abstinence increased significantly after ingestion of the substance and these effects were also observed at the 36-week follow up.[18]

Evaluation of high-dose psilocybin administration in 95 patients with alcohol use disorder was carried out in contrast to treatment with diphenhydramine. The doses of the substances used in this study were as follows: 25mg/70kg vs 50mg and 25-40mg/70kg vs 50-100mg (psilocybin and diphenhydramine respectively). Patients were subjected to motivational enhancement therapy and cognitive behavioral therapy. Percentage of heavy drinking days during the 32-week double-blind period was lower by 13,9% in the psilocybin group (amounting to 9,7% for these individuals while for the diphenhydramine group it reached 23,6%). The patients receiving the combination of psilocybin with psychotherapy reported better outcomes and fewer heavy drinking days in comparison to those ingesting diphenhydramine.[19]

An open-label pilot study including 15 psychiatrically healthy nicotine-smokers consisted in administering them with moderate (20mg/70kg) and high (30mg/70kg) doses of psilocybin during a 15-week protocol. On average, the participants had 6 previous quit attempts, smoked 19 cigarettes per day and had been doing so for 31 years. 80% of them were abstinent at the 6-month follow-up, a number rarely seen in the cessation rate in other therapies such as behavioral and/or pharmacological (usually their efficacy does not reach 35%).[20]

There are reports of psilocybin being effective in the treatment of other psychiatric disorders such as obsessive compulsive disorder (OCD), cluster headaches and AIDS-related demoralization.

One study on 9 subjects with DSM-IV-defined OCD consisted in their participation in up to

4 single-dose psychedelic-sessions. The administered doses ranged from sub-hallucinogenic to frankly hallucinogenic (the lowest being 100micrograms/kg, the highest 300microgram/kg). All the patients reported significant decreases in symptoms of their illness during one or more of the exposures to the substance.[21]

A survey gathered from 496 participants compared the use of indoleamine hallucinogens (psilocybin being among them) to conventional medication in the treatment of cluster headaches. Psychedelic substances were comparable or more effective than the latter, shortened the cluster periods and put the symptoms into remission with more frequency. Subjects reported that even rare ingestion and low doses of the substances mentioned above seemed to be efficacious in alleviating their pain.[22]

An open-label study published in "The Lancet" assessed the usefulness of psilocybin administration during therapy (psilocybin-assisted group therapy) in older long-term AIDS survivor men. The trial consisted of 8-10 therapeutic sessions during which the subjects were orally administered 0,3-0,36mg/kg of the substance. As a result, the level of demoralization diminished at the end of treatment and remained at a lower than the baseline level at the 3-month follow-up.[23]

Adverse effects

Although psilocybin has a large therapeutic index of 1:1000 and is generally safe and well-tolerated there are reports of side effects during the treatment with the abovementioned substance. They can be divided into physical and psychological as well as common and uncommon. Among the physical ones increased blood pressure, headache and nausea are frequent whereas fatigue, migraine, vomiting and physical discomfort occur less often. When it comes to psychological adverse effects the patients are most likely to experience anxiety and confusion. Strong or extreme fear, paranoia, psychotic-like symptoms and psychological discomfort are observed rarely. It is important to note that these effects are transient and limited to the time when one is under the influence of the drug for most of the patients. However serious the onset of psychotic illness can be it is most likely an expression of a pre-existing predisposition. Therefore, it is crucial to carry out thorough screening before qualifying individuals to be eligible subjects in studies concerning psychedelics.[24,25]

Contraindications

Keeping in mind that serious adverse effects such as a psychotic episode may occur during the administration of psilocybin there are some contraindications for its use. Among the ones mentioned most often are history of schizophrenia, psychosis, bipolar disorder and borderline personality.[26,27,28] During future studies a clear risk to benefit ratio should be established for treatment of patients with these conditions. Little is known about the administration of psychedelics to pregnant and breastfeeding women and therefore it is generally not recommended Because a transient raise in blood pressure and heart rate may occur during a therapeutic session involving psilocybin[29], cardiovascular conditions, especially those serious, untreated or poorly controlled, should also be considered as exclusion criteria in potential study subjects.

Conclusions

The use of psilocybin-assisted therapies seems to have great potential in the treatment of various psychiatric disorders, some of which are currently resistant to conventional treatment. Studies published in recent years suggest its safety and efficacy with minimal toxicity and good tolerance. It is crucial to provide patients with psychological support during and following the administration of the substance. It is equally important to screen the population for possible contraindications for ingesting psychedelics. More large-scale, well-designed studies with a long-term follow up period are required to unanimously prove the value of psilocybin in the treatment of psychiatric disorders.

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