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Unmet need in depression: Psilocybin, a breakthrough treatment option

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Abstract

Major depressive disorder (MDD) has become a health crisis of epidemic proportions in the modern world. One in six individuals in the world is experiencing an episode of major depression in his or her lifetime, and it is estimated that major depression will rank second after cardiac disease as a cause of international medical morbidity by the year 2020. Depression is associated with greater disability than are most other chronic illnesses and is a risk factor for mortality. Additionally, depression predicts the later development of a number of medical conditions, including cardiac and cerebrovascular disease, hypertension, diabetes, obesity, metabolic syndrome, dementia, and cancer. Unfortunately, most patients with depression do not experience a complete resolution of symptoms with antidepressant treatment. Partial-but incomplete-response to antidepressants is associated with an increased risk of full symptomatic relapse (even when on therapy) and a worse long-term disease course. Combined with the high prevalence and significant disability associated with MDD, the fact that currently available treatments are not fully adequate highlights the tremendous need to identify novel treatment strategies. In this review, we have compiled the information available about the potential of psilocybin in the treatment of MDD. This is recently called as breakthrough treatment by FDA. We have presented recent clinical study data to support the notion. This will surely help all health care practitioners to consider this drug in future for the treatment of their patients suffering with MDD.

Keywords: schizophrenia; bipolar disorder; depression; substance abuse disorder

Introduction

Disease and Unmet need

Depression is known to involve a complex and bidirectional interaction between the immune and nervous system^[1, 2]. Several studies showed that neurobiology of depression is not only linked with monoamines but also accompanied by an activation of inflammatory, auto-immune, and cell-mediated immune responses^[3]. In humans this condition arises from chronic medical conditions^[4]. On the other hand, in animals it can be induced by activation of the immune system with injection of endotoxins such as lipopolysaccharide (LPS)^[5]. These evidences provide the basis for the neuroinflammation theory of depression^[6]. Irrespective of the etiology of the depression, therapeutic strategy for the depression has two main drawbacks. These real unmet need in clinical practice are lack rapid acting antidepressant agents and management of treatment resistance depression are considered as. To develop more effective drugs, its crucial for clinician to focus on novel molecular targets outside of the monoamine system and to focus on enhancing neuroplasticity or alleviating neuroinflammation.

Psilocybin

Psilocybin is a psychedelic drug with hallucinogenic properties that was first isolated from the psilocybe strain of mushrooms in 1957. Colloquially, psilocybin is often called "magic mushrooms" or "shrooms." Psilocybin truffles are a lesser known "magic" fungus that contain very similar psychoactive substances as psychedelic mushrooms. Pharmacologically, psilocybin is the prodrug of psilocin (4-OH-dimethyltryptamine), a non-selective serotonin 2A receptor (5-HT_{2A}) agonist and classic a classic tryptamine hallucinogen and 'psychedelic' drug^[7]. Both compounds occur naturally in the 'psilocybe' genus of mushrooms, and are structurally related to the endogenous neurotransmitter serotonin (5-OH-tryptamine, 5-HT). Psilocybin has an ancient and more recent history of medicinal-use. Psilocybin is a strong agonist at 5-HT_{2A} as well as a moderate agonist at 5-HT_{1A} and 5-HT_{2C}^[8, 9]. Accumulating evidence suggests that psilocybin with accompanying psychological support can be used

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safely to treat a range of psychiatric conditions, including: end-of-life anxiety and depression ^[10], alcohol and tobacco addiction ^[11], obsessive compulsive disorder, and most recently from our group, treatment-resistant major depression ^[12]. Findings from healthy volunteer studies and trials with other psychedelics supplement those from clinical studies showing that these drugs can have a rapid and lasting positive impact on mental health, often after just one or two doses.

Pharmacological effects and Mechanism of action

Hallucinogenic effects typically onset within the first 20 to 40 minutes of use then disappear within 3 to 6 hours. Psilocybin's threshold for intoxication is approximately 40 mcg/kg of body weight. There is a low percentage of psilocybin in most mushroom varieties, so this corresponds to approximately 1 to 2 g of dried mushrooms ^[13]. This magic mushroom showed rapid, long lasting antidepressant and anxiolytic effects in humans as well as showed potential to assist psychotherapy for difficult-to-treat depression. Interestingly this effect was seen after only one or two acute treatment sessions. Recent studies suggested its therapeutic potential for end-of-life anxiety, OCD, smoking, alcohol dependence ^[8]. FDA recently calls this psychedelic a "Breakthrough Therapy" for severe depression. It acts as a serotonin receptor (5-HT_{2A}) agonist and hence has a novel pharmacology in the context of currently available antidepressant medications which are SSRI but not direct 5-HT_{2A} receptor agonists. Recent study in rats showed therapeutic efficacy of psilocybin more persistent than that of ketamine ^[14].

Psilocybin's first in depressed patients study and post-treatment brain effects suggested the 'reset' therapeutic mechanism of depression ^[8]. It is imperative that we gain a better understanding of the mechanisms through which psychedelics can, after only one or two treatments, produce positive and long-lasting antidepressant. All classic psychedelic compounds activate the serotonin 5-HT_{2A} receptor ^[8] and few has shown to activate the Akt/mTOR pathway ^[15]. One emerging promising therapeutic potential of psilocybin is its use as anti-inflammatory agent ^[16]. Psychedelics regulate inflammatory pathways via novel mechanisms and may represent a new and exciting treatment strategy for several inflammatory disorders. We consider role of psilocybin in the treatment of neuroinflammation based depression in rats or mice.

Results from clinical trials

The latest psilocybin clinical trial (2019) in 89 participants for twelve weeks assessed the effect of 10 mg of 25 mg of psilocybin. In this study, no serious adverse events from psilocybin were reported, drug didn't impair cognitive and emotional functioning and indicated the feasibility of administering psilocybin in a controlled setting to healthy participants with one-on-one therapist support. This clinical study reassuring and support further development of psilocybin as a treatment for patients with mental health problems that haven't improved with conventional therapy, such as treatment-resistant depression ^[17]. Two recent double-blind randomised control trials (RCTs) of psilocybin for depression and anxiety symptoms in a combined sample of 80 patients with life-threatening cancer found consistent safety and efficacy outcomes with those reported here ^[18, 19]. Psilocybin may play a role in reducing suicidality and improving mood although these patients did not necessarily

have a diagnosis of major depressive disorder. It also highlights the potential safety of the substance in such a large population ^[20]. A large percentage of the patients rated their psilocybin experience as one of the most meaningful experiences of their lives. As patient buy-in to therapy is important with mental health, this level of satisfaction with treatment may increase efficacy ^[21].

Safety of psilocybin

Furthermore, it is important to note that psilocybin's abuse potential is low ^[22]. In 2011, Studerus *et al.* compiled data from 8 different studies involving psilocybin administration from 1999 to 2008 ^[17]. This pooled analysis consisted of 110 healthy human subjects who received 1 to 4 different oral doses of psilocybin for a total of 227 psilocybin administrations. The doses used throughout the studies ranged from 45 mcg/kg to 315 mcg/kg. All subjects underwent extensive screening prior to entering the studies and were excluded if they had any active *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition* (DSM-IV) diagnosis or emotional liability. All the studies used the Altered States of Consciousness Rating Scale, which is a visual self-rating scale ^[17]. Short- and long-term safety was evaluated, and there was no indication of increased drug abuse, persisting perception disorders, prolonged psychosis, or other long-term deficits in functioning. The number of adverse reactions from psilocybin was few, resolved quickly, and was mostly associated with the highest doses of psilocybin. The subjects were followed for 8 to 16 months post psilocybin administration and exhibited no long-term negative side effects ^[20]. The safety demonstrated in this study opened the door for more research on psilocybin. It should be noted, however, that the administration of psilocybin in these studies followed strict protocols and therefore may lack external validity to the general population.

Breakthrough Therapy Designation

The designation of psilocybin as a Breakthrough Therapy for MDD acknowledges the unmet medical need in this broad population and the potential for significant improvements over existing therapies. The results from previous studies clearly demonstrate the remarkable potential for psilocybin as a treatment in MDD patients and confirmation is coming through clinical trials. Psilocybin potentially offers a novel paradigm in which a short-acting compound imparts profound alterations in consciousness and could enable long-term remission of depressive symptoms.

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