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TREATING DEPRESSION WITH PSYCHEDELICS

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Abstract

Depression is recognized as a substantial mental health problem in the general population. The symptomatology of this disease may vary, presenting a challenge for timely clinical diagnosis. Despite the variety of available therapeutic choices, a many do not respond to the prescribed treatment, and a significant number of patients develops chronic depression or even treatment-resistant depression (TRD). Such circumstances left limited treatment alternatives available, urging scientists to reconsider the usage of psychedelics. They have been used as a tool for shamanic healing, and after being criminalized in the second part of the twentieth century, they are slowly regaining recognition for their therapeutic potential. Their apparent molecular mechanism of action involves direct agonism of the serotonergic receptors, which have a high expression in the association cortex, responsible for cortical information integration and induced plasticity. Psilocybin, which has already passed phase II of clinical trials, is one of the most promising in TRD treatment. Several studies and meta-analyses have demonstrated strong evidence of TRD symptom relief when combined with psychedelic-assisted psychotherapy. This method has the potential to be a game-changer in the treatment of depression and TRD in neuropsychiatry. However, more multidisciplinary studies are needed to develop a deeper understanding of both treatment issues and future treatment options.

KEYWORDS: depressive disorder, neuropsychiatry, psilocybin, psychedelics, serotonin receptor, treatment-resistant depression

INTRODUCTION - CURRENT STATE OF DEPRESSION

Major depressive disorder (MDD) nowadays follows a dangerously rising trend of prevalence, already affecting 3.8% of the world population with a count of over 280 million people.[1] Practically one in five individuals will at some point in their life experience at least one episode of MDD. It is therefore estimated as the leading cause of disability and a prevalent mental health issue, contributing greatly to the overall global burden of disease.[1,2]

The onset of the first episode may vary, but it occurs most commonly in the mid-20s, being twice as prevalent in women than men.[2] MDD is usually characterized by depressed mood, despair, deficiency in interest, concentration, and pleasure even leading to the development of psychomotor retardation or agitation. Patients often experience low energy and appetite along with sleeping difficulties. MDD may have a gradual onset, but it is not uncommon for patients to experience sudden deterioration. The condition can aggravate to a point where the patient suffers suicidal thoughts, which may result in completed suicide if not recognized and treated timely. Clinicians face many challenges in adequate and prompt MDD diagnosis and treatment.[3]

Several therapeutic strategies are available for the treatment of MDD. The arsenal encompasses various psychotherapeutic approaches, as well as standard pharmacotherapy including monoaminergic, newer antidepressants and electromagnetic stimulation strategies. Regardless of diverse available treatment options, a significant proportion of patients fail to respond appropriately to the prescribed treatment.[2–4] To further complicate the situation, most of the patients face recurrent depressive episodes, with unpredictive duration, pattern or overall count of episodes. 80% of patients suffering MDD episodes with required psychiatric intervention will experience an iterant event, with rising tendency of recurrence with each new episode.[5] If treated, more than half of the patients might experience alleviation of their symptoms in 3–12 months, and regain sufficient functionality. However, this still leaves a substantial percentage (up to 27%) of patients developing a chronic MDD, or even a treatment-resistant depression (TRD).[2]

There is still no consensus regarding the exact definition of TRD. It is recognized as a heterogeneous phenomenon incorporating failure to respond to treatment and absence of remission following two or more medication attempts.[6,7] The available non-pharmacological follow-up treatment may consist of electrostimulation and repetitive transcranial magnetic stimulation, which, notwithstanding the acute improvement, do not show long term effects.[8] Due to the complexity of this disorder, the need for an individual treatment approach,[9] and challenges in the pharmacological and conservative approach, many pharmaceutical companies refrain from prioritizing further investment in drug development for TRD despite the crushing need for

adequate treatment of this illness.[10,11] This situation has left few possible therapeutic alternatives and has provided a new chance for an unusual treatment option that was, throughout history, left out of the picture.[12]

ANCIENT SUBSTANCES AS A POTENTIAL MODERN PSYCHIATRIC TREATMENT

Perception of hallucinogenic substances is nowadays in a so-called transitional phase. They have been perceived as tools for shamanic and spiritual healing practice since the earliest civilizations, and after suffering criminalization in the second half of the twentieth century, they are now slowly being recognized for their neurobiological therapeutic potential.[11] A meta-analysis published in 2016. regarding clinical studies of psilocybin administration for mood disorders has demonstrated positive results – 79% of patients showed substantial improvement after psilocybin treatment.[13]

However, their exact pharmacological properties are still being studied in the hopes of defining a specific mechanism of action responsible for clinical effects and potentially offering a new perspective on the background of mental disorders and deeper consciousness comprehension.[14] Their use is predominant in neuropsychiatric disorders resistant to conventionally available therapeutics, such as general anxiety disorder (GAD), obsessive-compulsive disorder (OCD), and of course MDD, especially for the patients suffering from end-of-life psychological distress, with a significant increase in the number of studies showing promising and long-lasting effects.[11,13]

MECHANISM OF ACTION

Commonly recognized under the incorrect term "hallucinogens", psychedelics are a class of psychoactive substances acting as perception alternating agents of real stimuli and should therefore be distinguished from substances that alter states of consciousness, like ketamine. In fact, there are three groups of psychedelics: tryptamines, prominently psilocin and dimethyltryptamine (DMT); lysergamines such as lysergic acid diethylamide (LSD); and phenethylamines (mescaline).

Their apparent molecular mechanism of action is obtained through serotonergic signaling pathways activated through direct serotonin 2A receptor agonism (5-HT2AR), which is why connections have been drawn to the possible treatment of MDD and anxiety.[15] 5-HT2ARs have a high expression in the association cortex, especially in layer 5 pyramidal neurons, which play a key role in cortical information integration and HT2AR induced plasticity.[16] Contrary to that, classic serotonin reuptake inhibitors (SSRIs) might even be mollifying such potential through post-synaptic 5-HT1A receptor binding, which

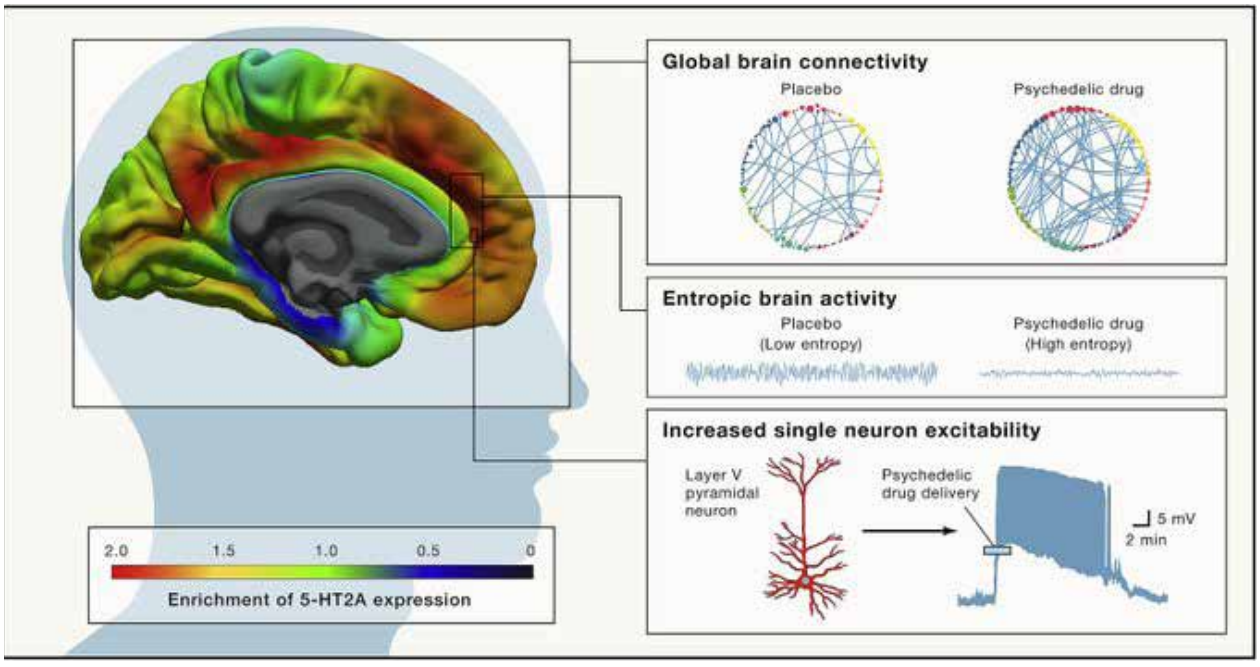


Figure 1. Alteration in brain regions integration and activity under the influence of Psilocybin.

The average density of 5-HT2AR differs across brain regions. Specific regions are presented as individual dots connected with lines if the activity is interpreted to be above the threshold of significance. Psilocybin shows substantial between-community (global) communication and connectivity, higher brain activity, and neuronal excitability when compared to placebo.

Source: Nutt D, Erritzoe D, Carhart-Harris R. Psychedelic Psychiatry's Brave New World. *Cell*. 2020;181(1):24-28. doi:10.1016/j.cell.2020.03.020. Copyright © 2020 The Authors. Published by the Elsevier Inc. Available under the CC BY 3.0 Unported license (https://creativecommons.org/licenses/by/3.0/).

results in diminished emotional moderation and limbic response, which is why psychedelics might be advantageous over SSRI in MDD treatment.[13]

Stimulation of layer 5 pyramidal neurons results in vast depolarization and subsequent immense modification of cortical signaling.[11] Activation of 5-HT5AR has been noticed to result in irregular excitation and loss of typical rhythmical activity due to asynchronous glutamate release, leading to transient disintegration and desegregation of the neuronal network.[16] The term "psychedelic state" has been used to describe this specific enhanced sensitivity to the environment, which is speculated to be underlying the positive outcomes of this therapeutic venture, emphasizing the achievement of emotional release.[13]

"Ego-dissolution" and a deep sense of "personal, interpersonal and existential oneness" are also some interesting concepts described as a potential explanation for patients' susceptibility to new insights into their memory, past behavior and a recalibration of pathological beliefs usually responsible for previous perception narrowing.[16] Pre-clinical studies have demonstrated the effects of psychedelics on the promotion of neural plasticity in circuits relevant for the treatment of neuropsychiatric disorders.[17] A scheme of the perceived level of neuronal global integration under the influence of psilocybin and similar psychedelics is shown in Figure 1.

The most important step in understanding the physiology of psychedelic impact on diverse functions and connectivity patterns of specific brain region is the development of neuroimaging techniques. An increment in sensory and somatomotor neural network interactions is detected along with a decrement of associative brain network interlinkage, allowing enhanced information processing and reduced rigid thinking patterns detected in a population of psychiatric disorders.[18] One such example includes decreased connectivity of the prefrontal cortex (PFC) and the parahippocampus, along with increased connectivity of PFC and inferior parietal cortex one day post psilocybin treatment, which have been shown to predict the treatment response 5 weeks post-treatment. More importantly, a phenomenon of amygdala activity alteration is also found to be an important therapeutic mechanism of psychedelics. Acute influence of psychedelics impacts the decrement of amygdala activity along with elevated PFC-amygdala connectivity, resulting in mitigated amygdala response to emotional stimuli, which might be underlying the normalization of negative cognitive bias observed in patients suffering from MDD.[19]

HIGH HOPES OR JUST GETTING HIGH

Psilocybin is a monoamine alkaloid naturally present in Psilocybe sp. mushrooms, obtaining its hallucinatory activity through its indole ring of the tryptamine structure shown in Figure 2. after being metabolized to psilocin with >40% activation efficacy. When administered orally, the onset of action is expected to be inside the window of 1-2 h, the plasma half-life of the psilocin is 2.5 h, with

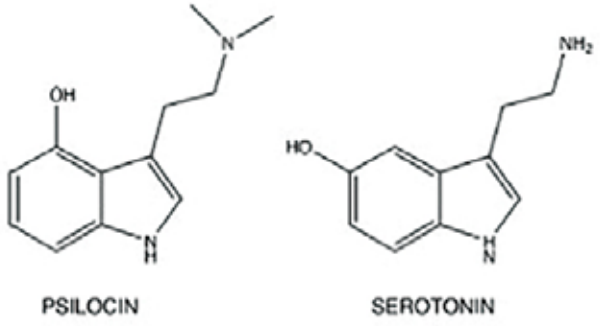


Figure 2. The resemblance of chemical structures of psilocin, the active metabolite of psilocybin with the serotonin molecule.

Source: Patra S. Return of the psychedelics: Psilocybin for treatment resistant depression. *Asian J Psychiatr.* 2016;24:51-52. doi:10.1016/j.ajp.2016.08.010
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the expected 3-4 h duration of the hallucinogenic effect.[20] High doses (0.3–0.6 mg/kg) usually cause sensory perception changes such as sensory illusion, synesthesia, and euphoria, and may be accompanied by nausea, vomiting and transient headaches.[21]

Among all psychedelics, psilocybin has shown the most potential in combating MDD and TRD, even reaching phase II of clinical studies. Double-blind controlled randomized trials have been investigating the effect of psilocybin on symptoms of MDD in patients with end-stage cancer and all have found psilocybin to have effective and long-term antidepressive and anti-anxiety effects post-treatment.[22–24] It is important to emphasize that most studies showing extremely positive effects of psilocybin on MDD were performed through psychedelic-assisted psychotherapy. which includes one or two therapists present during the session, which might last up to 6 h, followed by psychotherapy and analysis, helping patients talk through their experiences.[11,21]

Another positive aspect of such serotonergic psychedelics is the absence of withdrawal symptoms or compulsive drug-seeking behaviors, due to a lack of dopaminergic activity.[25] Furthermore, in contrast to a meta-analysis that revealed no significant effects of antidepressants compared to a placebo in depressive patients suffering from malignant diseases,[26] a growing body of evidence shows a notable alleviation of depressive symptoms when compared to placebo, with response maintenance of up to 60 days post-treatment, implying a stronger therapeutic effect of psychotherapy-assisted administration of psychedelics.[25] Challenges of sufficient blinding have been met in the search for an adequate placebo in the scrutinization of psychedelic therapeutic effects through the usage of an active placebo such as niacin. Niacin can induce mild cognitive and physiological changes, which is why it has been used in some studies, allowing the possibility of cross-over

trials. Patients have reported a reduction of anxiety, decline in the feeling of hopelessness and depressive symptoms, improvement of their overall quality of life, and some even described facilitated access to emotions and constant reduction of fear of death. [27]

While they might cause subtle sympathetic activity such as and transient emotional and cognitive alteration, no significant connections have been made to adverse mental health outcomes, no lasting side-effects nor physiological toxicity are detected, which is why they are generally considered safe. Therewithal, they appear to produce a prompt and lasting medicinal effect with a single or a few doses. However, individuals with a family history of psychosis are still being advised to avoid usage of this group of substances.[25]

CONCLUSION

One of the more significant recent strides in psychiatry has been the revival of therapeutic application of psychedelics. In the last few decades, several teams have begun clinical studies, which have yielded astonishing insights into brain activity and sparked an intriguing new approach to the psychedelic treatment of a variety of mental diseases, especially TRD. Many advantages of this novel therapeutic approach have been found in comparison to traditional antidepressants, especially the option of one-time drug administration for long-lasting medicinal and few adverse effects. The most prominent psychedelic used in MDD and TRD treatment is psilocybin, which has demonstrated a considerable improvement of MDD and TRD symptoms in controlled conditions of psychedelic-assisted psychotherapy approach. What is needed next are broad, multidisciplinary studies to better understand these therapeutics in future clinical practice.

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LIJEČENJE DEPRESIJE PSIHODELICIMA

Sažetak

Depresija je prepoznata kao značajan psihički problem u općoj populaciji. Simptomatologija ovog poremećaja je široka i predstavlja izazov za pravovremenu kliničku dijagnozu. Unatoč raznim dostupnim opcijama liječenja, mnogi ne postignu adekvatan odgovor na propisanu terapiju, razviju kroničnu depresiju ili čak depresiju rezistentnu na terapiju. Takve okolnosti rezultirale su ograničenim terapijskim opcijama te su prisilile znanstvenike na razmatranje alternativnih terapijskih opcija, poput psihodelika. Koristili su se u šamanskim obredima, a nakon kriminalizacije u drugoj polovici dvadesetog stoljeća, polako se prepoznaje njihov terapijski potencijal. Mehanizam djelovanja psihodelika uključuje direktni agonizam serotoninskih receptora koji su odgovorni za integraciju kortikalnih informacija i indukciju plastičnosti. Jedan od obećavajućih psihodelika za liječenje depresije rezistentne na terapiju je psilocibin koji pokazuje povoljne rezultate u drugoj fazi kliničkih testiranja. Više istraživanja i meta-analiza ukazuju na značajno olakšanje simptoma depresije rezistentne na terapiju korištenjem psihoterapije potpomognute psihodelicima. Ova metoda bi mogla biti prekretnica u liječenju depresije i depresije rezistentne na terapiju u neuropsihijatriji. Ipak je potrebno više multidisciplinarnih istraživanja kako bismo produbili razumijevanje terapeutskih problema i budućih mogućnosti liječenja.

KLJUČNE RIJEČI: depresija rezistentna na terapiju, neuropsihijatrija, psihodelici, psilocibin, serotoninski receptor, veliki depresivni poremećaj