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PERSPECTIVA/PERSPECTIVE

# Treating Major Depression Disorder with Psychedelics: A Potential Therapeutic Application for Psilocybin?

# Tratamento da Perturbação Depressiva Major com Psicadélicos: Uma Potencial Aplicação Terapêutica para a Psilocibina?

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## a. Major depressive disorder – a global health problem

Major depressive disorder (MDD) is a disabling psychiatric disorder, with the World Health Organization (WHO) estimating more than 300 million people are affected by this condition, and considering depression the single largest contributor to global disability, accounting for 10% of all years lived with disability.[1] Unfortunately, approximately one third of patients with MDD fail to respond to standard treatment, a condition known as treatment resistant depression (TRD), with great impact on patients and their families. Furthermore, common antidepressants may take too long to reach sustained clinical efficacy and, even in responders, there are significant relapse rates, highlighting the need to explore innovative treatments. While new antidepressant strategies have been approved to alleviate patient suffering, including transcranial magnetic stimulation and esketamine, psychedelics have also been recently considered as potential therapeutic options for MDD.

## b. What are psychedelics?

Psychedelics are substances that temporarily induce an altered state of mind, variably described as a combination of dissociation, perceptual distortions and mystical experience, among other effects. They act on the serotoninergic system, as 5-hydroxytryptamine 2A (5-HT2A) receptor agonists.[2] The term psychedelic was first used by the psychiatrist Humphrey Osmond in 1956, derived from Greek to mean 'mind manifesting'.[3] Not surprisingly, since their discovery by the scientific community, psychedelics were widely used in psychiatry for clinical and research purposes, until their legal prohibition in the 1960s.[3] Mescaline, dimethyltryptamine (DMT), lysergic acid diethylamide (LSD) and psilocybin are examples of psychedelics, the latter being the most promising for treatment of MDD.[2] Psilocybin is an indole alkaloid present in certain mushroom species, used by ancient cultures in religious rituals in order to induce a pleasant and positive spiritual/mystical experience.

## c. Treating major depressive disorder with psilocybin

Prior to their prohibition, therapeutic use of psychedelics, including psilocybin, was mainly motivated by their capacity to induce a "*transformative experience*" in patients diagnosed with then-called 'neurotic' disorders, leading to both short- and long-term improvements of symptoms,[2] including anxiety, depression and pain..[3] However, following legal restrictions to their use, and despite the encouraging results obtained previously, psychedelics were ignored for more than two decades. Only recently has the scientific community revisited psilocybin, mainly motivated by the

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need to develop new treatments options for depression. In 2011, a small cross-over placebo-controlled trial, in a cohort of 12 advanced-stage cancer patients, revealed trends towards reduction of depression and anxiety symptoms after psilocybin administration.[4] More recently, two more robust double-blind cross-over trials, with 51 and 29 participants, provided evidence of the significant antidepressant and anxiolytic effects of psilocybin in patients with cancer, when compared to active placebo.[4] Importantly, the effects reported in these three studies were immediate and sustained after psilocybin. In 2018, a first open-label study attempted to investigate feasibility, safety, and efficacy of psilocybin in TRD, with authors reporting no major adverse effects, while depressive symptoms markedly reduced at 1 week, 3 months and 6 months after psilocybin.[4] Noteworthy, the overall pre-post effect size in the reduction of depressive symptoms among the patients who received psilocybin was approximately 1.5, when considering the four aforementioned trials.[4] More recently, Davis and colleagues, in a randomized waiting list-controlled study (n=27), further supported treatment efficacy and safety of psilocybin administration in patients diagnosed with MDD, with a remission rate larger than 50%,[5] while Carhart-Harris and colleagues have shown that two doses of psilocybin were as effective as escitalopram.[6]

## d. What are the mechanisms of action of psilocybin?

While there is increasing data regarding its clinical efficacy, the antidepressant mechanisms of psilocybin are still unknown. It is known that psilocybin acts as serotonin agonist, producing effects on cognition, perception and emotion.[2]Specifically, it modifies cortical excitability and reactivity through 5HT-2A receptor agonism.[2] Furthermore, there is evidence that 5HT-2A agonism, is associated with neuroplastic phenomena such as increases of neuron branching and of the number and length of dendrites.[7] These findings are consistent with one of the most well accepted pathophysiological theories for MDD, namely the impairment of brain neuroplasticity, i.e., capacity to generate, maintain, migrate, and integrate neurons/neuronal activity. According to this theory, neuroplasticity is decreased in MDD, producing changes in behavior, cognitions and emotions that characterize this disorder. Psilocybin, through 5HT-2A agonism, may revert these processes, resulting in long-lasting antidepressant effects.[7]

At the brain network level, interesting but somewhat counterintuitive findings have been reported. After acute psilocybin administration in healthy individuals, the medial prefrontal cortex (mPFC) and anterior cingulate cortex (ACC) were less positively functionally connected to posterior cingulate cortex when compared to placebo, as shown in resting-state functional magnetic resonance imaging (rs-fMRI), while the cerebral blood flow (CBF) decreased, a finding that was associated with intensity of reported effects for psilocybin.[8] However, in patients diagnosed with TRD, after psilocybin administration, ventral mPFC was more functionally connected to inferior lateral parietal cortex, an effect that was predictive of treatment response at 5-weeks, as was decreased functional connectivity between prefrontal cortex and para-hippocampus and decrease in amygdala CBF.[9] Decreased activity in the amygdala, as well as the para-hippocampus, is consistent with previous findings in rs-fMRI and event-based fMRI studies after treatment with selective serotonin reuptake inhibitors. However, in similarly designed studies, psilocybin increased amygdala responses to emotional stimuli among patients with TRD.[10] Interestingly, some have argued that psilocybin may work as a reset mechanism at brain network level, supported by findings of disintegration of Default Mode Network, a canonical resting state brain network associated to consciousness, thought to underlie psychological effects of psychedelics described as "ego dissolution". As claimed by the authors, such resetting process would subsequently enable resumption of normal functioning, ultimately leading to the ability to resolve negative stimuli.[8-10] This hypothesis has been supported by recent findings that reported changes in personality traits following psilocybin therapy, namely a decrease in neuroticism and increase extraversion and openness.

## e. Future perspectives

Interest in psilocybin therapeutic effects, mainly for depression treatment, has grown. Research have been developed to clarify its pharmacological properties, neurobiological impact, psychological and behavioral effects, and most importantly, its therapeutic antidepressant mechanisms.[2] Recent studies highlight that psilocybin is a safe and potentially effective option for depression, but there is consensus that more robust and carefully designed randomized controlled studies are necessary in this field. In fact, the available evidence is mostly based in trials that were either open-label or had a cross-over or waiting--list controlled design, leading to possible confounders and bias. Furthermore, the follow-up periods were short, not allowing for conclusions about long-term efficacy, the dose that should be used is still unclear, and the need for concomitant psychotherapy is unresolved. Importantly, multi-center randomized control trials using psilocybin are being conducted in Europe, including Portugal, and North America, to answer some of these questions. Nevertheless, the encouraging results obtained to date, particularly if confirmed by current ongoing trials, will certainly drive the scientific and clinical communities, as well as policy makers, to further develop this important field of research.

**Responsabilidades Éticas**

**Conflitos de Interesse:** AJO-M foi coordenador nacional para Portugal de um estudo não intervencionista (EDMS--ERI-143085581, 4.0) para caracterizar uma Coorte de Depressão Resistente ao Tratamento na Europa, patrocinado pela Janssen-Cilag, Ltd (2019-2020), é destinatário de uma bolsa da Schuhfried GmBH para normatização e validação de

testes cognitivos, e é coordenador nacional para Portugal de ensaios de terapia com psilocibina para depressão resistente ao tratamento, patrocinado por Compass Pathways, Ltd (EudraCT 2017-003288-36 e 2020-001348-25 ) e de esketamina para depressão resistente ao tratamento, patrocinado por Janssen-Cilag, Ltd (EudraCT: 2019-002992-33). Nenhuma das agências acima mencionadas teve um papel na preparação, revisão ou aprovação do manuscrito, nem na decisão de enviar o manuscrito para publicação. Os autores restantes declararam que não têm conflitos de interesse potenciais envolvendo este trabalho, incluindo atividades financeiras relevantes fora do trabalho submetido e quaisquer outros relacionamentos ou atividades que os leitores possam perceber como tendo influenciado, ou que dêem a aparência de potencialmente influenciar o que está escrito.

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## Ethical Disclosures

**Conflicts of Interest:** AJO-M was national coordinator for Portugal of a non-interventional study (EDMS-ERI-143085581, 4.0) to characterize a Treatment-Resistant Depression Cohort in Europe, sponsored by Janssen-Cilag, Ltd (2019-2020), is recipient of a grant from Schuhfried GmBH for norming and validation of cognitive tests, and is national coordinator for Portugal of trials of psilocybin therapy for treatment-resistant depression, sponsored by Compass Pathways, Ltd (EudraCT number 2017-003288-36 and 2020-001348-25), and of esketamine for treatment-resistant depression, sponsored by Janssen-Cilag, Ltd (EudraCT NUMBER: 2019-002992-33). None of the aforementioned agencies had a role in the preparation, review, or approval of the manuscript, nor in the decision to submit the manuscript for publication. The remaining authors have declared that they have no potential conflicts of interest involving this work, including relevant financial activities outside the submitted work and any other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing what is written.

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