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TRABALHO FINAL
MESTRADO INTEGRADO EM MEDICINA

Clínica Universitária de Psiquiatria e Psicologia Médica

Psilocybin-assisted therapy as an option for Treatment-Resistant Depression: a narrative review

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Junho'2021

RESUMO

A Depressão Resistente ao Tratamento é um dos outcomes do Transtorno Depressivo Major e está associada uma baixa qualidade de vida e a um maior uso de cuidados de saúde. Evidência científica demonstrou que a psilocibina, um psicadélico clássico agonista do recetor 2A de serotonina, pode ser usado como uma opção terapêutica no tratamento de diversas doenças psiquiátricas. Este trabalho tem como propósito providenciar uma revisão integrativa da atual evidência científica sobre o uso da psilocibina como opção terapêutica no tratamento da Depressão Resistente ao Tratamento. As seguintes bases de dados foram pesquisadas de 1 de janeiro de 2010 a 1 de maio de 2021: PubMed, Multidisciplinary Association for Psychedelic Studies' (MAPS) Psychedelic Bibliography e CochraneLibrary. Apenas estudos com o objetivo de avaliar os efeitos da psilocibina em pacientes com uma idade superior a 18 anos e com o diagnóstico de Depressão Resistente ao Tratamento foram incluídos. Estudos com placebo, placebo ativo e outros tratamentos como modelos comparativos foram incluídos. Nove estudos foram incluídos. Em linha com a evidência científica anterior, o benefício do tratamento com psilocibina não está apenas associado a uma redução dos sintomas depressivos, mas também a outros efeitos como mudanças na personalidade, perspetivas, comportamentos e um bem-estar psicológico geral. Uma análise qualitativa dos pacientes submetidos ao tratamento confirma os resultados quantitativos. A psilocibina parece atuar de uma forma diferente, mas complementar aos antidepressivos clássicos. A nível neurobiológico parece criar um mecanismo de 'reset'. A psilocibina poderá ser usada no futuro como uma opção terapêutica no tratamento da Depressão Resistente ao Tratamento. No entanto, a confirmação através de estudos randomizados controlados com placebo utilizando uma amostra mais vasta serão necessários.

Palavras-chave: Depressão Resistente ao Tratamento; Psilocibina; Default Mode Network; recetor de serotonina; entropia cerebral.

Treatment-Resistant Depression is one of the outcomes of Major Depression Disorder and is associated with lower health related quality of life, greater work productivity and activity impairment and increased healthcare resources utilization. Evidence has shown that psilocybin, a classic 5-HT2AR agonist psychedelic, can be used in the treatment of several mental disorders, including Major Depressive Disorder. The purpose of this paper is to provide an integrative review and offer novel insights regarding the use of psilocybin as a treatment option for Treatment-Resistant Depression. The PubMed, Multidisciplinary Association for Psychedelic Studies' (MAPS) Psychedelic Bibliography and CochraneLibrary online databases were searched from January 1st of 2010 to May 1st of 2021. Only clinical trials evaluating the effects of psilocybin on patients, older than 18 years old, with a diagnosis of Treatment-Resistant Depression were included. Clinical trials with placebo, active placebo and previous medications as comparison models were

included. Nine studies formed the review. As previous evidence has shown, the benefits of treatment with psilocybin may not be only related to a reduction in depressive symptoms, but to broader effects like changes in personality, perspectives, behaviors, and psychological wellbeing overall. A qualitative analysis of the patients that underwent this treatment confirmed the quantitative results. Psilocybin appears to act in a different but complementary way of classic antidepressants and at a neurobiological level it seems to work through a 'reset' mechanism. Psilocybin seems to be a possible future treatment option for Treatment-Resistant Depression. However, this needs confirmation from well-designed placebo controlled randomized trials employing a large sample size.

Keywords: Treatment-Resistant Depression; Psilocybin; Default Mode Network; serotonin receptor; brain entropy.

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INTRODUCTION

According to the DSM-5 criteria, major depressive disorder (MDD) has very well-established criteria. Its treatment can lead to different outcomes, one being Treatment-Resistant Depression (TRD). However, a consensual definition for TRD is yet to be determined (Gaynes et al., 2020). The most common definition is a case of MDD with a minimum of two treatment failures with confirmation of prior adequate dose and duration of treatment (Gaynes et al., 2020). Compared to non-treatment resistant depression and the general population, patients with TRD are associated with lower health related quality of life (HRQoL), greater work productivity and activity impairment (WAPI), and increased healthcare resources utilization (HRU) (Jaffe et al., 2019)There has also been data reporting significant economic burden in patients with this clinical status (Johnston et al., 2019).

Treatment for this condition is involved in a lot of controversy. Different approaches have been considered (Pandarakalam et al., 2018; Voineskos et al., 2020). Option treatments include the combination of more than one type of disease specific treatment, augmentation, meaning the use of a non-antidepressant treatment with an antidepressant drug, electroconvulsive therapy (ECT), transcranial magnetic stimulation, vagal nerve stimulation, psychodynamic and cognitive-behavioral therapies and even alternative medicines and complementary therapies, like hypnotherapy. New treatment options for TRD like ketamine, psilocybin and anti-inflammatory drugs like cyclooxygenase-2 inhibitors, infliximab and allopregnanolone have emerged recently. Even with this broad spectrum of therapeutic options, treatment of TRD remains merely empirical. Careful planning and monitoring should be used when considering a multidimensional approach using pharmacotherapy, neuromodulation and psychotherapy, especially with novel treatment options.

Modern clinical trials show strong evidence that therapy with psilocybin could be used as a treatment for different mental disorders like MDD (Davis et al., 2021), substance use disorders (de Veen et al., 2017; Bogenschutz et al., 2015; Johnson et al., 2014; Johnson et al., 2017), cancer-related anxiety and depression (Grob et al., 2011; Griffiths

et al., 2016; Ross et al., 2016) or obsessive-compulsive disorder (Moreno et al., 2006). There have also been several studies showing positive changes in attitudes and behaviors towards life caused by psilocybin in a short (Griffiths et al., 2006; Griffiths et al., 2008; MacLean et al., 2011) and long term (McGlothin et al., 1971; Doblin et al., 1991; Studerus et al., 2011). The focus of this work is to review the potential use of psilocybin-assisted therapy as a treatment option for TRD.

Brief history of psychedelics

The word "psychedelic" comes from the Greek for "mind-manifesting", since they reveal the inner workings of people's minds (Osmond et al., 1957). They have been used in ancient cultures for millennia, probably longer than any other drug (McGuire et al., 1982; Carod-Artal et al., 2015; Nichols & Walter et al., 2020)

After the discovery of LSD in the 1930s, and its approval for research in the early 1950s, there was a remarkable explosion of research on psychedelic drugs. It is important to state that the conditions of the clinical trials carried out during this time, were insufficient regarding its methods. Groups were not well defined, control groups or blind study teams were often absent, treatments were inconsistent, outcomes and adverse effects were not reported, treatment groups were inadequately and inconsistently defined and outcomes, adverse effects and statistical analysis were often absent (Rucker et al., 2018). Nonetheless, these clinical studies were vital for the evidence of the use of these drugs in psychiatry. However, its recreational use outside the laboratory setting, led to a huge anti-psychedelics backlash (Stevens et al., 1987), culminating in the classification of these drugs in the Schedule 1 category in 1967, meaning that it has no currently accepted medical use as treatment, there is a lack of accepted safety for use of the drug under medical supervision and it has high potential for abuse. This status, along with the loss of funding from governments led to an extinction of psychedelic research (Belouin & Henningfield et al., 2018; (Rucker et al., 2018) – (Figure 1).

For years, the research done on psychedelics was considered a closed chapter, being only recently reviewed at the turn of the XX century (Rucker et al., 2018) . Since this psychedelic 'renaissance' has emerged, several randomized clinical trials (RCTs) focusing on high socio-economic burden, morbidity, mortality and with no effective treatments,

like treatment-resistant depression, have been published (Andersen et al., 2021; Rucker et al., 2018) to separate these drugs effects from its context. It is important to mention that no serious adverse effects have been reported yet (Johnson et al., 2008). However, some argue that a consolidated database of adverse event information is necessary for the approval of these drugs, since these trials, especially with psilocybin, are known for not collecting data in a systematic manner (Rucker et al., 2018).

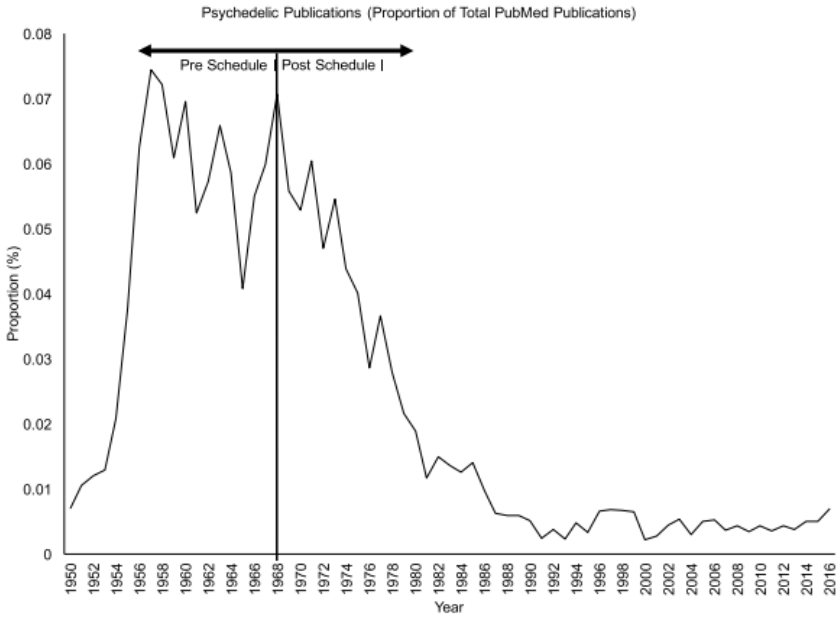

Figure 1: The effect of Schedule I on psychedelic drug research. Number of PubMed publications in which a classical psychedelic drug is found in the title expressed as a proportion of all PubMed publications, by year, from 1950 to 2016.
Rucker, J., Iliff, J., & Nutt, D. J. (2018). Psychiatry & the psychedelic drugs. Past, present & future. *Neuropharmacology*, *142*, 200–218. https://doi.org/10.1016/j.neuropharm.2017.12.040.

Psilocybin

Classical psychedelics can be subdivided into three groups: lysergamines, like LSD (lysergic acid diethylamide), phenethylamines, like mescaline, and tryptamines, like psilocybin (O-phosphoryl-4-hydroxy-N,N-dimethyltryptamine) (Nichols et al., 2004) – (Figure 2).

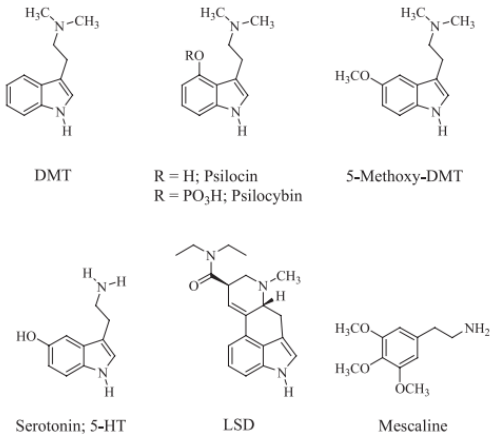

Figure 2: Structural formula for serotonin (5-HT) and different psychedelics

Nichols D. E. (2004). Hallucinogens. *Pharmacology & therapeutics*, *101*(2), 131–181. https://doi.org/10.1016/j.pharmthera.2003.11.002.

Metabolism and pharmacokinetics

Psilocybin is a naturally occurring alkaloid that can be found in the so-called “magic mushrooms”. It is a prodrug that is dephosphorylated to psilocin in the intestinal mucosa (Horita, A., & Weber, L.J. et al., 1961). After absorption, psilocybin is distributed in all tissues, including the brain, where it exerts its psychedelic properties. Orally, with approximately a dose above 15 mg, the effects start after 20-40 minutes, reach their peak around 60-90 minutes and last for about 4-6 hours after the administration (Hasler et al., 1997; Passie et al., 2002). Intravenously, the effect starts in 1-2 minutes, peaks after 4-5 minutes and lasts for 20 minutes (Carhart-Harris et al., 2011; Hasler et al., 1997).

Pharmacodynamics

Psilocybin acts in several different pathways, but since it is structurally related to serotonin (Hasler et al., 1997; Nichols et al., 2004)- (Figure 2), its psychoactive effects are primarily associated with its 5HT2A receptor (5-HT2AR) agonism (Stenbæk et al., 2021; Nichols et al., 2004); Glennon et al., 1984). In fact, like most hallucinogens, its affinity to the serotonin 5-HT2AR is correlated with its potency (Glennon et al., 1984).

Furthermore, the higher the percentage of occupancy of the receptors, the stronger the intensity of the subjective effects of psilocybin (Madsen et al., 2019). These changes can be blocked by the antagonism of the 5-HT2AR (Vollenweider et al., 1998), reinforcing the idea that the subjective effects caused by this substance come from a 5-HT2AR agonism. In humans, the distribution of 5-HT2AR is generally high throughout the cortex (Pazos et al., 1987) but is densest in multi-nodal, high-level association regions (Belliveau et al., 2017; Erritzoe et al., 2009; Carhart-Harris, Erritzoe, et al., 2012). In terms of the cortex's laminar organization, 5-HT2AR are expressed particularly in the apical dendrites layer Va of the cortex (Weber & Andrade et al., 2010), key cortical information-integration units (Larkum et al., 2009). These neurons are the primary source of output from a cortical region and a subsequent projection to hierarchically subordinate regions (Spruston et al., 2008). Also, we know that throughout 5-HT2AR signaling, psychedelics, including psilocybin, open a window of neuroplasticity (Vaidya et al., 1997; Ly et al., 2018; Boulougouris et al., 2008; Carhart-Harris & Nutt et al., 2017).

Psychotropic, neuropsychological and somatic effects

The subjective effects caused by psilocybin can be rather difficult to describe. However, individuals submitted to this drug in clinical trials describe common drowsiness and alterations of the pre-existing mood state at low doses (Hasler et al., 2004). Higher doses cause distorted perception of time and space, changes in sensory perception (geometric and complex visual hallucinations, colorful illusions, synesthesia and changed meaning of percepts) and auditory perception (hypersensitivity to noises), derealization, altered perception of the "self" or "ego", depersonalization and magical thinking (Geyer & Vollenweider et al., 2008; Hasler et al., 2004). Although most of the experiences are described as *"pleasurable"*, *"magical", "mystical"* and as one of the most personally meaningful and spiritually significant (Hasler et al., 2004; Griffiths et al., 2006; Griffiths et al., 2008), in some individuals psilocybin can induce anxiety, sensation of fear, loss of control (Geyer & Vollenweider et al, 2008); Hasler et al., 2004).

As somatic effects, psilocybin has a predominant sympathetic activity, causing mydriasis, increase in heart rate and in blood pressure (Hasler et al., 2004). It can also cause

dizziness, weakness, tremor, nausea and vomiting, drowsiness, yawning, paresthesia, blurred vision and increased tendon reflexes (Hollister et al., 1961; Johnson et al., 2008).

Risks and side effects

In a paper rating 20 drugs (Nutt et al., 2010) - (Figure 3), including stimulants, depressants, opioids and psychedelics, on 16 criteria: 9 related to the user, and 7 related to the harm that the drug causes on others, psilocybin-containing mushrooms were classified the less harmful.

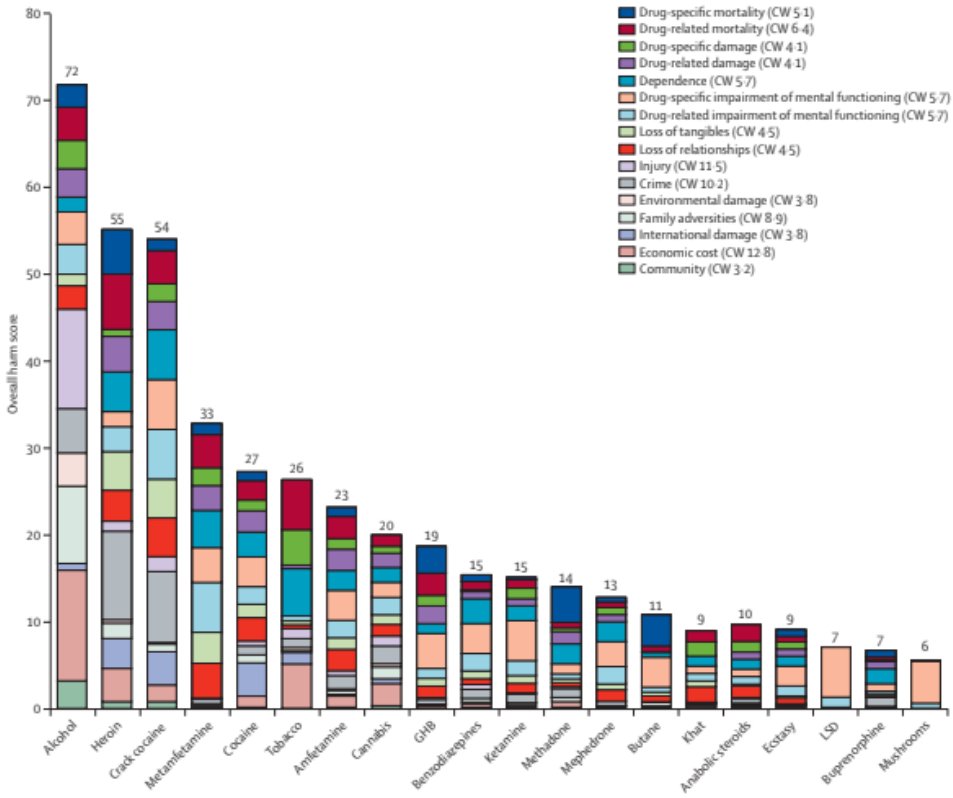

Figure 3: Overall weighted scores for each of the drugs.

Nutt, D. J., King, L. A., Phillips, L. D., & Independent Scientific Committee on Drugs (2010). Drug harms in the UK: a multicriteria decision analysis. *Lancet (London, England)*, *376*(9752), 1558–1565. https://doi.org/10.1016/S0140-6736(10)61462-6.

Psilocybin has a very low toxicity level (Nichols et al., 2004; Passie et al., 2002) and it's virtually impossible to die from an overdose of it, since it would be necessary to eat approximately 19 grams of the pure drug or consume their body weight in fresh psilocybin containing mushrooms to bring on death (www.erowid.org). On the other

hand, in the clinical trial examined in this review doses do not surpass 25mg (Carhart-Harris, Bolstridge, et al., 2016). It is also important to state that this drug does not cause addiction, since it does not affect the mesolimbic dopaminergic pathway that activates the reward system (Nichols et al., 2004; O'Brien et al., 2006), as well as craving or withdrawal symptoms (O'Brien et al., 2006). Also, chronic use is related to a decrease in the number of 5-HT2ARs, which leads to a rapid onset of short-lasting tolerance (Roth et al., 1998).

Around 2,000 subjects received psilocybin in a controlled environment during psychological and psychiatric research by 2005 (Metzner et al., 2005), without causing any serious side effects (Johnson et al., 2008). Main side effects described in trials include anxiety, paranoid experiences, derealization, depersonalization, long lasting unpleasant experiences (bad trips), psychotic reactions and hallucinogen persisting perception disorder (HPPD) (Strassman et al., 1984; Johnson et al., 2008). Usually, psychological interventions are sufficient and anxiolytics and/or atypical antipsychotics can be used in extreme and rare situations (Johnson et al., 2008; Strassman et al., 1994). Also, psilocybin can cause symptoms of serotonin syndrome but only in doses superior to the ones used in clinical trials (Klock et al., 1975). During the history of use of psilocybin-containing mushrooms, there are no records of somatic toxicity (Hofmann et al., 2005) and organ damage only occurs when confusion between psilocybin-containing mushrooms and other morphologically similar mushrooms is made (Franz et al., 1996). Although uncommon, there is still a risk that psilocybin can trigger psychotic symptoms in patients with an already premorbid mental illness. However, more research needs to be done in order to understand if psychosis would occur in the absence of the hallucinogenic experience or if it represents an early onset that would occur anyway (Strassman et al., 1984; Grinspoon and Bakalar et al., 1981). Since psilocybin induces a state of altered perception with the intensification of emotions, dangerous behavior may occur, like aggression to self and others (Strassman et al., 1984). There have been reported cases of people taking their lives under the influence of psychedelics, but only in uncontrolled circumstances and not related directly to its toxicity (Amsterdam et al., 2011; O'Brien et al., 2006). In fact, dangerous behaviors can occur with psychedelics in these non-medical situations, due to the altered perception, hallucinations and intensified emotions caused by them (Johnson et al., 2008). Nevertheless, these

complications can be significantly reduced by educating an individual, creating a safe environment and building rapport with an experienced intoxication guide (Johnson et al., 2008).

The Default Mode Network, psilocybin effects and Depression

The default mode network (DMN) has become a hot topic in cognitive neuroscience and several reasons justify its relevance in this area (Guldenmund et al., 2012). Regions in this network receive more blood flow (Zou et al., 2009) and consume more energy (Raichle & Snyder, 2007) and have a highest expression of 5-HT2A receptors (Beliveau et al., 2017), when compared to other areas in the brain. These regions are considered centers of dense connectivity (Hagmann et al., 2008), therefore serving as *connector hubs* for integration and routing of information (van den Heuvel et al., 2012). Alongside with this, during a transient period of functional connectivity within the DMN, coupling with other brain areas also happens (de Pasquale et al., 2012). This is something that other brain networks do not do (de Pasquale et al., 2012; Braga et al., 2013), implying that the DMN serves as a central *orchestrator* of global function in the brain, being the highest level of functional hierarchy (Carhart-Harris & Friston et al., 2010).
At a functional level, this network is not involved in sensory processing and stimulus-dependent thought (Sepulcre et al., 2012), but rather, is activated during higher-level, metacognitive functions such as self-reflection and introspection (Qin & Northoff et al., 2011), autobiographical remembering, prospection, theory-of-mind reasoning (Spreng & Grady et al., 2009) and mental time-travel (Buckner & Carroll et al., 2007; Andrews-Hanna et al., 2010; Martin et al., 2011). Furthermore, the resting-state functionality of the DMN correlates with internal awareness (Vanhaudenhuyse et al., 2010), rumination in depression (Berman et al., 2011; Zhou et al., 2020) and neuroticism (Adelstein et al., 2011). Curiously, psilocybin has been found to decrease activity and connectivity in brain regions of the DMN (Carhart-Harris, Erritzoe, et al., 2012) that are over-engaged in depression (Greicius et al., 2007; Berman et al., 2011) but normalized by a broad palette of effective treatments (Goldapple et al., 2004; Mayberg et al., 2005; Kennedy et al., 2007; William Deakin et al., 2008).

Psilocybin-assisted therapy

It becomes important to state that therapy with psychedelics must not be seen as pure pharmacotherapy, but more as a distinct form of (drug-assisted) psychotherapy. We need to understand that these experiences can be extremely challenging and sometimes, bring painful memories from the past (Barrett et al., 2016), so the way we approach them is of key importance. Although different protocols of psychedelic therapy have been used across different studies, they all follow the same basic premises (Johnson et al., 2008). Normally, this therapy involves three stages: preparation, the psychedelic session itself and integration afterwards. To approach the experience with little resistance as possible, since letting go fully allows the most benefit, preparation becomes crucial for maximizing the potential of the psychedelic session (Carhart-Harris, Roseman, et al., 2018). On the other hand, integration is important to process the events that occurred during the session, learn valuables lessons from them and furthermore incorporate these messages into daily life (Richards et al., 2017). Here, we will be focused on the protocol used in the trials with psilocybin for TRD (Watts & Luoma, 2020; (Carhart-Harris, Bolstridge, et al., 2016) – (Figure 4).

First, patients were screened via telephone interview according to outlined criteria. The inclusion criteria were moderate to severe major depression (17 or more points on the HAM-D scale) and no improvement despite the use of two adequate courses of antidepressant treatment of different classes for at least 6 weeks within the current depressive episode. Exclusion criteria were a diagnosed psychotic disorder or an immediate family member with this diagnosis, a medical condition conditioning unsuitability for the study, history of mania or serious suicide attempts, blood or needle phobia, a positive pregnancy test and a current drug or alcohol dependence. During the trial, the team concluded that a suspected borderline personality disorder should be added as an exclusion criterion (R. L. Carhart-Harris, Bolstridge, et al., 2018), since it is a psychiatric condition judged to be incompatible with establishment of rapport with therapy team and/or safe exposure to psilocybin.

Candidates meeting the criteria were invited to do a second screening at the facilities where the sessions would take place. This step consisted of a written informed consent, a detailed evaluation of the patients' physical and mental (using the MINI-5

questionnaire) background, different baseline assessments and a thorough physical examination, including an ECG, routine blood tests, blood pressure, heart rate, physical examination and urine tests for drugs of abuse and pregnancy when necessary.

Once evaluated, patients did a baseline functional MRI followed by a preparatory session. The purpose of this session was to know the patients' background and history as well as providing information about the experience under psilocybin, discussing its effects and simulating some aspects of the dosing sessions. This was followed by two dosing sessions separated by one week. The first session, where patients received a low oral dose of psilocybin (10mg), was a preparation for the following session where patients would create rapport with the therapists and lower their anxiety for the next session. The second dose, a high oral dose of 25mg, was the one the team predicted as having long lasting therapeutic effects. After the ingestion, in both sessions, patients would close their eyes and listen to music. During the entire session, psychiatrists would adopt a non-directive, supportive approach, allowing the patient to experience an uninterrupted introspection. One day after the high-dose session, patients did a second functional f-MRI and completed different questionnaires.

The follow-up period was done at different timelines until 6 months after the high-dose session. The follow-up consisted in the conduction of several questionnaires and assessments as well as an integration component. This last one involved non-judgmental listening of the patients' testimony of the experience, occasional interpretation of the experience and its meaning and advice regarding the changes felt by patients in their lives.

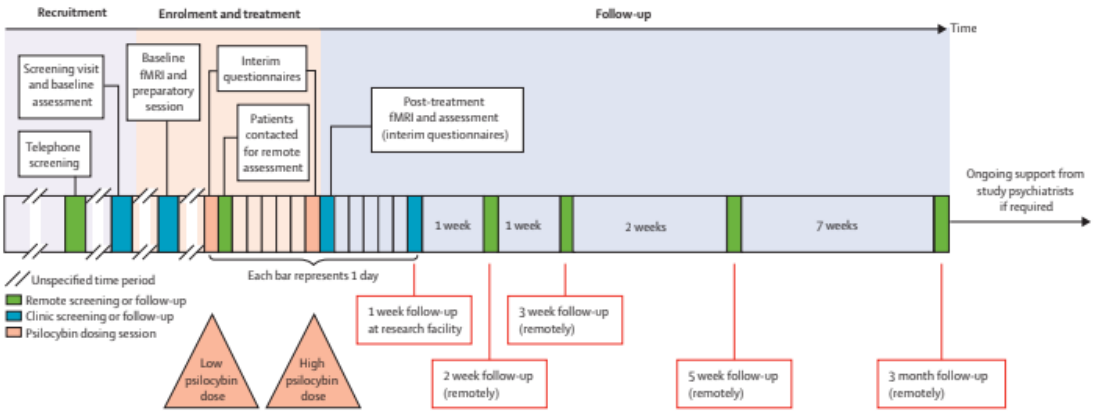

Figure 4: Schedule of study interventions of psilocybin for TRD.

Carhart-Harris, R. L., Bolstridge, M., Rucker, J., Day, C. M., Erritzoe, D., Kaelen, M., Bloomfield, M., Rickard, J. A., Forbes, B., Feilding, A., Taylor, D., Pilling, S., Curran, V. H., & Nutt, D. J. (2016). Psilocybin with psychological support for treatment-resistant depression: an open-label feasibility study. *The lancet. Psychiatry*, *3*(7), 619–627. https://doi.org/10.1016/S2215-0366(16)30065-7.

METHODS

The following review was conducted according to the 2009 PRISMA Guidelines.

Search Strategy

The PubMed, Multidisciplinary Association for Psychedelic Studies' (MAPS) Psychedelic Bibliography and CochraneLibrary online databases were searched using the following keywords: *Psilocybin* OR *Psilocybin/therapeutic use* AND *Depression* OR *Depressive Disorder* OR *Treatment-Resistant Depression* OR *Major Depression.* Literature search was restricted to the period from January 1st of 2010 to May 1st of 2021. Only studies published in English were included.

Eligibility criteria

For the purpose of this review, only clinical trials evaluating the effects of psilocybin on patients, older than 18 years old, with a diagnosed treatment-resistant depression were included. Systematic and narrative reviews, case reports, papers and letters focused on the above-mentioned terms were excluded.

Clinical trials with placebo, active placebo and previous medications as comparison models were included.

RESULTS

(All studies but R. Carhart.Harris et al., 2021 were part of the open-label study that took place in 2016 (Carhart-Harris, Bolstridge, et al., 2016). Full details of trial procedures have been described in pages 13-14).

Psilocybin on the reduction of depressive symptoms

An open-label study involving 12 patients with TRD that received two doses of psilocybin in a controlled setting, sought to investigate the safety and feasibility of psilocybin administration in this group, as well as to evidence an initial proof of its efficacy (Carhart-Harris et al., 2016). There was no control group. In this case, the primary outcome measure to evaluate feasibility were patients' self-rated subjective intensity of psilocybin effects, reported on a 0-1 scale. To evaluate the efficacy of psilocybin in TRD patients, mean changes in the severity of self-reported depressive symptoms were measured using the 16-item QIDS (Quick Inventory of Depressive Symptoms) questionnaire (Rush et al., 2003), from baseline to 1 week after the high-dose session of psilocybin. QIDS was also assessed at 2, 3 and 5 weeks and 3 months. Safety was assessed through clinical monitoring and interview follow-ups during and after the sessions. Also, changes in the BDI (Beck Depression Inventory) (Beck et al., 1961), STAI-T (Spielberger's State-Trait Anxiety Inventory) and SHAPS (Snaith-Hamilton Pleasure Scale) (Snaith et al., 1995) scales were assessed between baseline, at 1 week and at 3 months of follow-up, and changes in the HAM-D (Hamilton Depression Rating scale), MADRS (Montgomery-Åsberg Depression Rating Scale) and GAF (Global Assessment of Functioning) clinician-rated scores were assessed between baseline and 1 week of follow-up.

Mean self-rated intensity was 0.51 (SD 0.36) for the low-dose session and 0.75 (SD 0.27) for the high-dose session. Relative to baseline, depressive symptoms were markedly reduced 1 week (mean QIDS difference –11.8, 95% CI –9.15 to –14.35, p=0.002, Hedges' g=3.1) and 3 months (–9.2, 95% CI –5.69 to –12.71, p=0.003, Hedges' g=2) after the high-dose and maximum effects were felt at 2 weeks (–12.9 95% CI –10.64 to –15.6, p=0·002, Hedges' g=3.2) - (Figure 5).

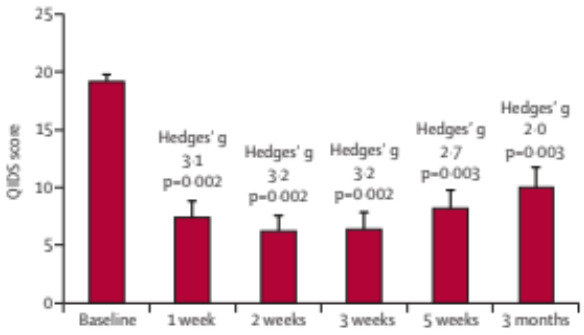

Figure 5: Mean depression severity (QIDS) over time. QIDS scores of 16–20 are considered severe depression, scores of 11–15 are considered moderate depression, scores of 6–10 are considered mild depression and scores of 5 and less are considered absent depression.

Carhart-Harris, R. L., Bolstridge, M., Rucker, J., Day, C. M., Erritzoe, D., Kaelen, M., Bloomfield, M., Rickard, J. A., Forbes, B., Feilding, A., Taylor, D., Pilling, S., Curran, V. H., & Nutt, D. J. (2016). Psilocybin with psychological support for treatment-resistant depression: an open-label feasibility study. *The lancet. Psychiatry*, *3*(7), 619–627. https://doi.org/10.1016/S2215-0366(16)30065-7.

Eight (67%) of the twelve patients met criteria for complete remission (a score of ≤9 on the BDI) at one week and seven (58%) continued to meet criteria for response (50% reduction in BDI score relative to baseline) at three months. Five of these seven (42%) patients were still in complete remission at this endpoint (Figure 6).

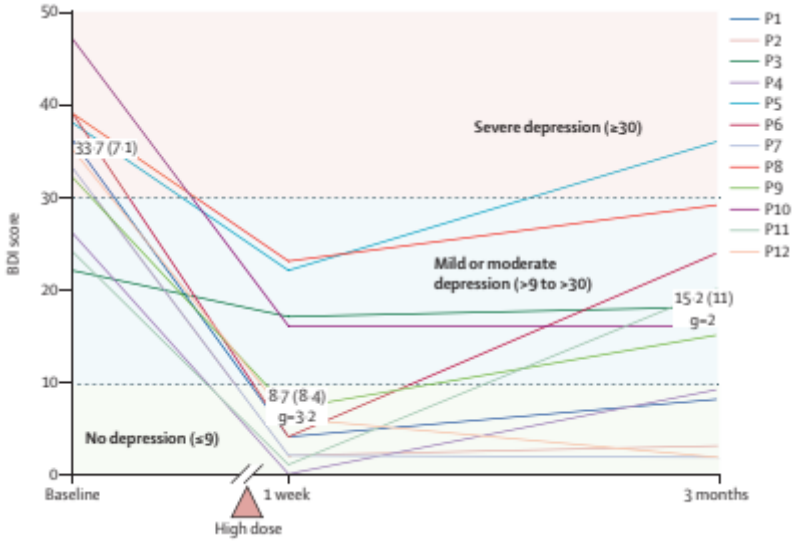

Figure 6: Depression severity (BDI) over time, by patient.

Carhart-Harris, R. L., Bolstridge, M., Rucker, J., Day, C. M., Erritzoe, D., Kaelen, M., Bloomfield, M., Rickard, J. A., Forbes, B., Feilding, A., Taylor, D., Pilling, S., Curran, V. H., & Nutt, D. J. (2016). Psilocybin with psychological support for treatment-resistant depression: an open-label feasibility study. *The lancet. Psychiatry*, *3*(7), 619–627. https://doi.org/10.1016/S2215-0366(16)30065-7.

Anxiety (STAI-T) and anhedonia (SHAPS) related scores were both reduced at 1 week and 3 months after the high dose. The intensity of the experience was well tolerated by all patients, no major adverse effects were assessed and no tranquilizing medication (oral lorazepam and risperidone) was required. Most common adverse effects were transient anxiety (n=12), transient confusion or thought disorder (n=9), transient nausea (n=4), transient headache (n=4) and transient paranoia (n=1). However, these were expected effects of psilocybin.

The same team did a second study increasing the number of patients from 12 to 20 and extending the time of follow-up time from 3 to 6 months (R. L. Carhart-Harris, Bolstridge, et al., 2018) This time, the only primary outcome considered was mean changes in QIDS scores. These were measured at baseline, 1-3 and 5 weeks and 3 and 6 months post-treatment. BDI and STAI-T scores were measured at 1 week and at 3 and 6 months. SHAPS was measured at 1 week and at 3 months and clinician-rated scores HAM-D and GAF at one week.

Relative to baseline, QIDS scores were significantly reduced at all six post-treatment time points, with the maximum effects felt at 5 weeks (− 9.2, 95% CI = − 11.8 to − 6.6, t = − 7.2, $p < 0.001$, Cohen's d = 2.3). Changes in HAM-D showed a reasonable correspondence with changes in QIDS data across the same period. BDI and STAI-T scores were reduced at 1 week, 3 months and 6 months. SHAPS scores were reduced at 1 week and at 3 months and HAM-D and GAF scores were reduced at 1 week. Also, reductions in depressive symptoms in the QIDS score at 5 weeks were predicted by the quality of the acute psychedelic experience, measured by the 11 dimension altered states of consciousness (11D ASC) questionnaire (Studerus et al., 2010;Dittrich et al., 1998). This self-rated instrument captures the acute quality of the psychedelic experience and covers factors such as insightfulness, blissfulness, experience of unity, and spirituality. In line with the previous report from the same trial, treatment was well tolerated and no serious side effects occurred. Again, most common adverse effects

were transient anxiety (n=15), transient headaches (n=8), transient nausea (n=5) and transient paranoia (n=3). Except for one patient, no patients received additional treatments within 5 weeks of the high-dose session.

Psilocybin versus Escitalopram for Depression

Although selective serotonin-reuptake inhibitors (SSRIs) are first line treatment for MDD, they usually take several weeks to work and, in some patients, they don't even induce a response (Cipriani et al., 2018). As reported above, psilocybin has shown to induce a lasting response in patients with TRD, but direct comparisons between these two treatments are lacking. To better understand this, a phase 2, double-blind, randomized, controlled trial involving patients with long-lasting, moderate-to-severe major depressive disorder compared psilocybin with escitalopram, an SSRI, over a period of 6 weeks (Carhart-Harris et al., 2021).

Through randomization, patients were assigned in a 1:1 ratio to receive either two separate doses of 25 mg of psilocybin 3 weeks apart over a period of 6 weeks, while receiving a microcrystalline cellulose placebo capsule daily (psilocybin group), or two separate doses of 1 mg of psilocybin 3 weeks apart over a period of 6 weeks, while receiving 10mg of escitalopram in the first 3 weeks and 20mg in the next 3 weeks (escitalopram group). Psychological support was given to all patients through the entire process. The primary clinical output was the change on the QIDS-SR-16 from baseline to 6 weeks. Secondary outcomes included response at 6 weeks according to the QIDS-SR-16 (defined as a decrease in score of ≥50% from baseline); remission at 6 weeks according to the QIDS-SR-16 (defined as a score of 0 to 5); change in the score on the 14-item QIDS-SR (QIDS-SR-14) from the day before to the day after dosing-day 1; and the changes from baseline to week 6 in the scores on the Beck Depression Inventory 1A (BDI-1A), the 17-item Hamilton Depression Rating Scale (HAM-D-17), the Montgomery and Asberg Depression Rating Scale (MADRS), the Flourishing Scale (FS), the Spielberger's Trait Anxiety Inventory (STAI), the Brief Experiential Avoidance Questionnaire (BEAQ), the Work and Social Adjustment Scale (WSAS), the Snaith Hamilton Anhedonia Pleasure Scale (SHAPS), the Warwick-Edinburgh Mental Wellbeing Scale (WEMWBS) and the Suicidal Ideation Attributes Scale (SIDAS), as well as the scores

at 6 weeks on the Psychotropic-Related Sexual Dysfunction Questionnaire (PRSexDQ). To assess post-treatment side effects and other phenomena associated with psilocybin and escitalopram, an investigator-constructed scale - the Post-Treatment Changes Scale (PTCS) - was used as a safety outcome. Adverse effects were recorded every visit from dosing-day 1 until week 6.

The mean change from baseline in the score on the QIDS-SR-16 at week 6 was −8.0±1.0 in the psilocybin group and −6.0±1 in the escitalopram group. Response occurred in 70% of the patients in the psilocybin group and in 48% of those in the escitalopram group, for a between-group difference of 22 percentage points and remission occurred in 57% and 28%, respectively, for a between-group difference of 28 percentage points. Although the results from these outcomes seem to favor psilocybin, no significant difference between the groups was observed. The other secondary outcomes generally favored psilocybin over escitalopram, but unfortunately the confidence intervals for the between-group differences were not adjusted for multiple comparisons (Figure 7).

Table 2. Primary and Secondary Outcomes.*

Outcome	Psilocybin (N=30)	Escitalopram (N=29)	Difference (95% CI)†
Primary			
Change in QIDS-SR-16 score at 6 wk — points	−8.0±1.0	−6.0±1.0	−2.0 (−5.0 to 0.9)‡
Secondary			
Depression-related outcomes			
Change in QIDS-SR-14 score from the day before to the day after dosing-day 1 — points	−5.7±0.9	−2.8±0.9	−3.0 (−5.5 to −0.4)
QIDS-SR-16 response at 6 wk — no. (%)§	21 (70)	14 (48)	22 (−3 to 48)
QIDS-SR-16 remission at 6 wk — no. (%)¶	17 (57)	8 (28)	28 (2 to 54)
Change in HAM-D-17 score at 6 wk — points	−10.5±1.0	−5.1±1.0	−5.3 (−8.2 to −2.4)
Change in MADRS score at 6 wk — points	−14.4±1.7	−7.2±1.7	−7.2 (−12.1 to −2.4)
Change in BDI-1A score at 6 wk — points	−18.4 (−22.6 to −13.8)	−10.8 (−14.3 to −7.3)	−7.6 (−13.3 to −1.8)
Change in WEMWBS score at 6 wk — points	15.4±1.9	7.3±1.9	8.1 (2.6 to 13.5)
Change in FS score at 6 wk — points	14.4±1.7	9.0±1.7	5.4 (0.5 to 10.3)
Change in STAI score at 6 wk — points	−17.6±2.2	−8.5±2.2	−9.0 (−15.2 to −2.8)
Change in BEAQ score at 6 wk — points	−10.5±2.2	−1.0±2.3	−9.5 (−15.9 to −3.1)
Change in WSAS score at 6 wk — points	−9.7±1.7	−3.8±1.7	−5.8 (−10.7 to −1.0)
Change in SHAPS score at 6 wk — points	−4.7±0.6	−2.5±0.6	−2.2 (−3.8 to −0.6)
Change in SIDAS score at 6 wk — points	−2.0 (−4.3 to 0.0)	−0.8 (−3.4 to 2.0)	−1.3 (−6.5 to −0.3)
PRSexDQ score at 6 wk	0 (0 to 0)	3 (0 to 7)	−2 (−4 to 0)
LEIS score at 6 wk	4.1±0.9	−2.2±1.0	6.3 (3.6 to 9.0)

Figure 7: Primary and Secondary Outcomes.

Carhart-Harris, R., Giribaldi, B., Watts, R., Baker-Jones, M., Murphy-Beiner, A., Murphy, R., Martell, J., Blemings, A., Erritzoe, D., & Nutt, D. J. (2021). Trial of Psilocybin versus Escitalopram for Depression. *The New England journal of medicine*, *384*(15), 1402–1411. https://doi.org/10.1056/NEJMoa2032994.

It is important to note that patients in the psilocybin group reported greater perceived improvements in the ability to cry and feel compassion, intense emotion and pleasure, and reported feeling less drowsy than those in the escitalopram group. No serious adverse events, visual perceptual changes, psychotic symptoms, or dependency-related behaviors were observed in both groups.

Patients' perception of psilocybin as a treatment

When it comes to new therapeutic approaches, a qualitative analysis may be important for clarifying their underlying mechanisms (Braun & Clarke et al., 2013). Therefore, information about the volunteers' experience may act as a complement to quantitative data on the same subject. Concerning psychedelic-based treatment, much of the work done has its focus on the clinical outcomes and little has been done to better understand the underlying psychological mechanisms of these therapies.

To better understand the effects of psychedelic treatment on depression, patients that underwent a clinical trial of psilocybin-assisted therapy for TRD were interviewed about the experience 6 months after the session (Watts et al., 2017).

Patients described depression as a feeling of disconnection (from their senses, themselves, others and the world around them) and a sensation of being "trapped in their minds", with the process of rumination reported by all. After the sessions, there was a shift towards a feeling of reconnection. Patients mentioned feelings of self-worth and self-compassion, reported engaging in past activities and hobbies, described improvements in their sensory capacities, discovered new values and perspectives, strengthened bonds with their loved ones and felt a deep connection to the world around them. Most of them also described a sudden change in the quality of their consciousness, reporting a sense of "mental freedom", unlike the previous "mental prison" feeling.

Before the treatment, patients felt like their emotions were being avoided or repressed, as well as past trauma. Unlike their daily lives, the dosing sessions were an intense "cathartic" experience that led to the surrender to emotions and past trauma. After the treatment, one frequent change described was a long-lasting openness to emotional

experience that lasted even when the symptoms of depression came back. Less impulsive behavior and a new sense of calm, patience and responsibility regarding difficult situations were also described.

When compared to psilocybin-assisted therapy, a recurrent theme reported about traditional and previous treatments was that these reinforced the disconnection and avoidance felt by depression. Talking therapies, like cognitive behavioral therapy (CBT), or antidepressants seemed to promote a sort of psychological pain that should be suppressed, rather than explored as a symptom of an underlying problem. On the other hand, psychedelic therapy promoted a capacity for self-reflection, where patients were able to access their pain and past traumas more easily.

Effects of psilocybin on patients' personality

Treatment of depression with antidepressants has been shown to modulate facets of one's personality (Costa et al., 2005). One of the extraordinary effects of psychedelics is their capacity to have persisting impact on personality and outlook (Mcglothlin et al., 1971; Studerus et al., 2011). Regarding sessions with these substances, a single dose of psilocybin or LSD has shown to increase the *Openness* personality facet in healthy volunteers (MacLean et al., 2011; Carhart-Harris, Kaelen, et al., 2016) and DMT users are associated with more *Openness* scores than naive controls (Barbosa et al., 2016). However, there is little evidence if personality traits of depressed patients can be modulated by psychedelic-assisted therapy.

A study with patients suffering from TRD aimed to explore if this therapy would modulate personality parameters (Erritzoe et al., 2018). These were assessed using the NEO-PI-R instrument (Costa et al., 1992), which covers 5 domains: *Neuroticism, Extraversion, Openness to Experience, Conscientiousness* and *Agreeableness,* each one containing six facets. NEO-PI-R raw scores were standardized as T-scores (M = 50, SD = 10) and baseline vs. 3-month follow-up NEO-PI-R scores were compared. To evaluate the subjective experience under psilocybin the ASC questionnaire was used. QIDS inventory was employed to assess depressive symptoms at baseline and at selected time points. A standard threshold for defining treatment response (≥50% reduction in QIDS score from baseline) was used to separate patients into responders and non-responders.

From baseline to the 3-month follow-up, *Neuroticism* scores decreased (T-score change: 5.7, P = 0.002), *Extraversion, Openness* and *Conscientiousness* (slightly) increased (T-score changes: 6.5, P < 0.001, and 4.9, P = 0.012 and P = 0.086 respectively) and *Agreeableness* scores did not change (Figure 8).

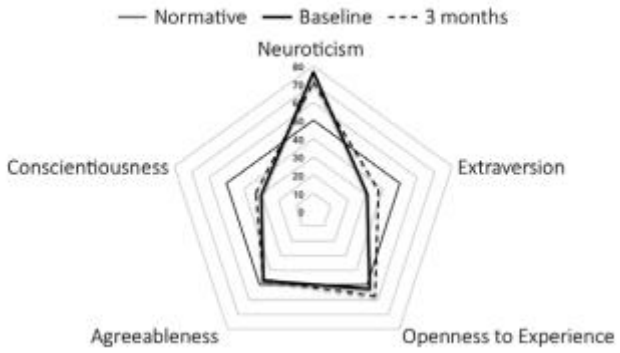

Figure 8: Trait T-scores scores at baseline (solid thick line) and at 3-month follow-up (dotted line).
Erritzoe, D., Roseman, L., Nour, M. M., MacLean, K., Kaelen, M., Nutt, D. J., & Carhart-Harris, R. L. (2018). Effects of psilocybin therapy on personality structure. *Acta psychiatrica Scandinavica*, *138*(5), 368–378. https://doi.org/10.1111/acps.12904.

When comparing clinical responders (n=7) to non-responders (n=12) at 3 months, *Neuroticism* score had decreased more from baseline to 3-month follow-up among responders than among non-responders (-23 +/- 17 vs. -6 +/- 8 respectively, P = 0.038), whereas *Conscientiousness* score had increased more among responders than among non-responders over the same period (15 +/- 11 vs. 0 +/- 12 respectively, P = 0.017). Regarding the other 3 personality domains, responders did not differ significantly from non-responders. Furthermore, none of the 5 NEO-PI-R domain changes from baseline to 3-month follow-up significantly correlated with change in either QIDS or BDI depression scores at 3 months. Furthermore, the degree of insightfulness experienced during the high-dose session was associated with a reduction in *Neuroticism* score (r = 0.47, P = 0.043) and an increase in *Extraversion* score (r = 0.54, P = 0.017).

Anticipation of life events

Patients suffering from depression have an unrealistic perspective of themselves and the world (Beck et al., 1967; Beck and Rush et al., 1979) and, when compared to healthy

individuals, these patients tend to feel hopeless and pessimistic (Peterson & Seligman et al., 1984; Hollon et al., 1986; Beck et al., 1988; Hill et al., 1989), creating a negative bias when predicting future life events (Strunk et al., 2006; Strunk & Adler et al., 2009). In contrast to this, feelings of optimism and wellbeing have been found in individuals after the administration of psychedelics (Griffiths et al., 2006; Griffiths et al, 2008; Grob et al., 2011; MacLean et al., 2011; Carhart-Harris et al, 2016).

To understand if the pessimism bias regarding future life events could be alleviated by psilocybin, a study compared treatment-resistant patients that underwent psilocybin-assisted therapy with healthy non-treated controls (Lyons & Carhart-Harris, 2018). Both groups performed the Prediction of Future Life Events (POFLE) task (Strunk et al., 2006), where individuals predict the probability of life events occurring within 30 days, after which the rate of the events occurrence is determined (Figure 9). To evaluate depressive symptoms, the self-reporting BDI inventory was used (Beck et al., 1961).

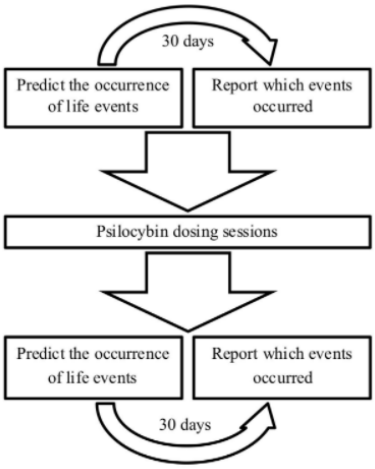

Figure 9: Schematic diagram of the study design.

Lyons, T., & Carhart-Harris, R. L. (2018). More Realistic Forecasting of Future Life Events After Psilocybin for Treatment-Resistant Depression. *Frontiers in psychology*, *9*, 1721. https://doi.org/10.3389/fpsyg.2018.01721.

At baseline, patients showed a pessimism bias [$t(14) = -3.260$, $p = 0.006$; 95% CI (−0.16, −0.03), $g = 1.1$], related to the depressive symptoms measured by the BDI inventory ($rs = -0.55$, $p = 0.017$). One week after the psilocybin session, the pessimism bias decreased significantly to control levels [$t(14) = -2.714$, $p = 0.017$; 95% CI (−0.21, −0.02), $g = 0.7$] and the BDI scores significantly decreased [$t(14) = 7.900$, $p < 0.001$; 95% CI (16.17, 28.23), g

= 1.9]; moreover, the magnitude of change in both variables was significantly correlated ($r = -0.57$, $p = 0.014$). Also, patients after treatment expected more desirable than undesirable life events [$t(14) = 3.485$, $p = 0.004$; 95% CI (0.92, 3.88), $g = 1.3$] and became more accurate predicting the future [$t(14) = 1.857$, $p = 0.042$; 95% CI (−0.01, 0.12), $g = 0.6$], whereas no such change was observed in the control subjects.

Psilocybin and improvement of emotional face recognition

Patients with depression are thought to exhibit a negative bias in emotional processing of face stimuli, thus contributing to their low mood (Harmer et al., 2009). Treatment SSRIs and SNRIs is associated with a reduction in this negative bias (Harmer et al., 2003; Harmer et al., 2009), and it produces a bias towards happy faces in healthy individuals (Harmer et al, 2003; Norbury et al., 2009). These changes are fundamental for the clinical effects these drugs (Warren et al., 2015) and are predictive of clinical outcome (Tranter et al., 2009; Shiroma et al., 2014). On the other hand, psilocybin acutely attenuates the recognition of negative faces, but not positive or neutral ones (Kometer et al., 2012) and enhances psychological and brain responses to positive autobiographical memories (Carhart-Harris, Leech, et al., 2012) in healthy volunteers.

The cognitive and emotional bias mechanism in depression can be a possible explanation through which psilocybin reduces depressive symptoms. However, no study has explored whether psilocybin can produce long-term changes in emotional face processing in depressive patients and if these are correlated with changes in symptoms. In consideration of these things, a study tried to demonstrate whether psilocybin could alter patients' emotional processing biases, comparing treatment-resistant depression patients that underwent psilocybin-assisted psychotherapy with healthy control volunteers (Stroud et al., 2018). Both carried out a dynamic emotional recognition task called Dynamic Emotional Expression Recognition Task, or DEER-T (Platt et al., 2010), at baseline and one week after the high-dose session. At the same time points, the participants also completed QIDS and SHAPS inventories.

Before treatment, depressed patients showed longer reaction times to recognize all emotion types when compared with controls ($p < 0.001$). After treatment, an

improvement in the reaction time of depressed patients was observed, with no significant difference between this group and the control group (p = 0.208) - (Figure 10). Emotion recognition was faster 1 week post-treatment compared with baseline in patients (p = 0.004, d = 0.876) but not controls (p = 0.263, d = 0.302).

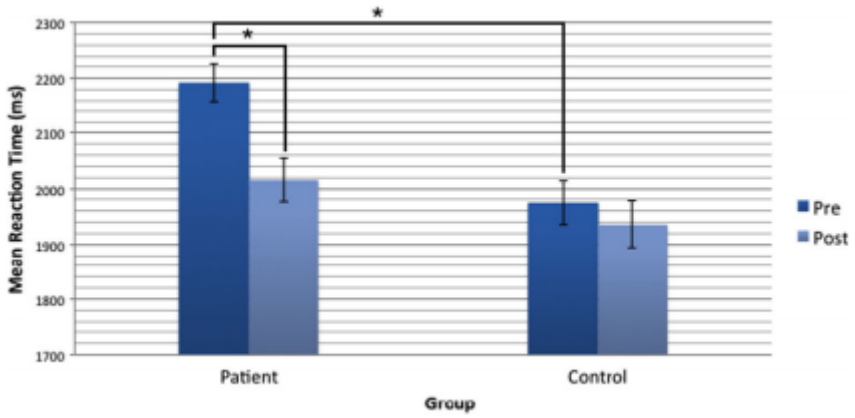

Figure 10: Mean reaction time to correctly respond to all emotions on the DEER-T task in patients and controls.

Stroud, J. B., Freeman, T. P., Leech, R., Hindocha, C., Lawn, W., Nutt, D. J., Curran, H. V., & Carhart-Harris, R. L. (2018). Psilocybin with psychological support improves emotional face recognition in treatment-resistant depression. *Psychopharmacology*, *235*(2), 459–466. https://doi.org/10.1007/s00213-017-4754-y

Also, a significant positive correlation between faster reaction times and improvements in the anhedonia score SHAPS post-treatment were detected (r = 0.640, p = 0.010) - (Figure 11). However, this correlation was not found between the performed emotional processing task and the QIDS score for depressive symptoms (r = − 0.073, p = 0.796).

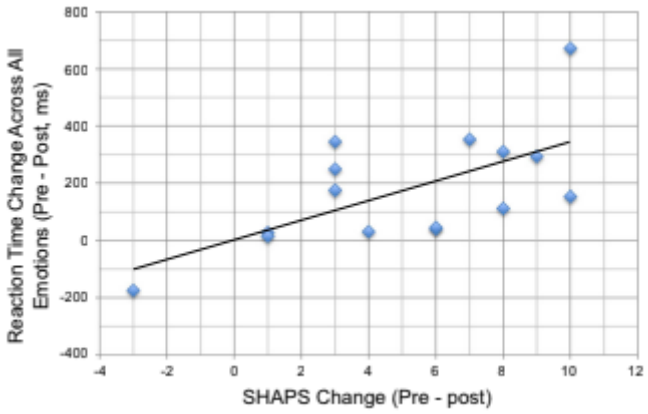

Figure 11: Change in reaction time to all emotions correlated with change in SHAPS score in depressed patients receiving psilocybin-based treatment.

Stroud, J. B., Freeman, T. P., Leech, R., Hindocha, C., Lawn, W., Nutt, D. J., Curran, H. V., & Carhart-Harris, R. L. (2018). Psilocybin with psychological support improves emotional face recognition in treatment-resistant depression. *Psychopharmacology*, *235*(2), 459–466. https://doi.org/10.1007/s00213-017-4754-y.

fMRI-measured brain mechanisms with psilocybin treatment

Most of the neuroimaging studies regarding the effects of psychedelics in humans are focused in their acute 'psychedelic state' (Carhart-Harris, Erritzoe, et al., 2012; (Carhart-Harris, Muthukumaraswamy, et al., 2016). Although this evidence is important to the better understanding of how psychedelics affect our brains, few studies contain results from the post-acute effects of psychedelics (Sampedro et al., 2017) and their anatomical changes in the long term related to their use (Bouso et al., 2015; Erritzoe et al., 2011).
To better understand these post-acute effects, a study using functional magnetic resonance imaging (fMRI) measured the changes in cerebral blood flow (CBF) and resting state functional connectivity (RSFC) before and one day after treatment-resistant depression patients were treated with psilocybin (Carhart-Harris et al., 2017). Since the days after the experience, referred to as the "after-glow", have been associated with mood improvements (Winkelman et al., 2014; Majić et al., 2015), the purpose of the study was to see if these changes related to the so called "after-glow" would correlate to immediate and to a 5-week endpoint on clinical outcomes. To evaluate patients' symptoms the QIDS-16 questionnaire was used.

A reduction of CBF in the amygdala in whole-brain analyses was observed, and it reached significance in the left Heschl's gyrus, left precentral gyrus, left planum temporale, left superior temporal gyrus, left amygdala, right supramarginal gyrus and right parietal operculum. Reduction in the amygdala CBF showed a significant correlation with reduced depressive symptoms (r=0.59; p=0.01) – (Figure 12)

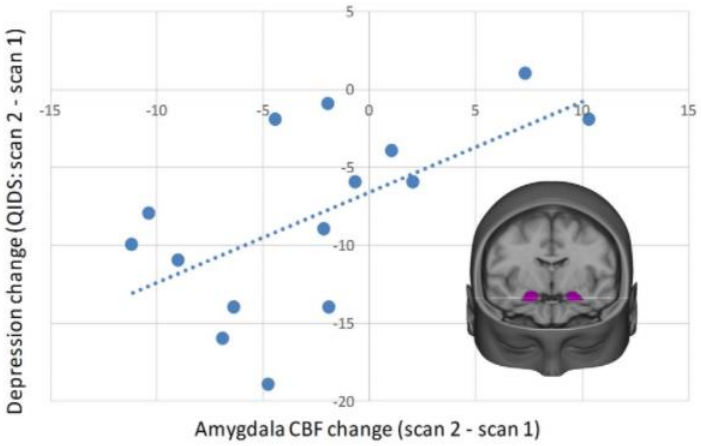

Figure 12: Post-treatment changes in bilateral amygdala CBF versus changes in depressive symptoms (r=0.59, p=0.01).

Carhart-Harris, R. L., Roseman, L., Bolstridge, M., Demetriou, L., Pannekoek, J. N., Wall, M. B., Tanner, M., Kaelen, M., McGonigle, J., Murphy, K., Leech, R., Curran, H. V., & Nutt, D. J. (2017). Psilocybin for treatment-resistant depression: fMRI-measured brain mechanisms. *Scientific reports*, *7*(1), 13187. https://doi.org/10.1038/s41598-017-13282-7.

Regarding RSFC analyses, an increased integrity was observed within the DMN one-day after the treatment. Increased ventromedial prefrontal cortex (vmPFC RSFC) was observed with the bilateral inferior-lateral parietal cortex (ilPC) post-treatment and the vmPFC-ilPC RSFC coupling predicted treatment response at 5 weeks, with responders showing significantly greater vmPFC-ilPC RSFC increases than non-responders (t=2.1; p=0.03) – (Figure 13).

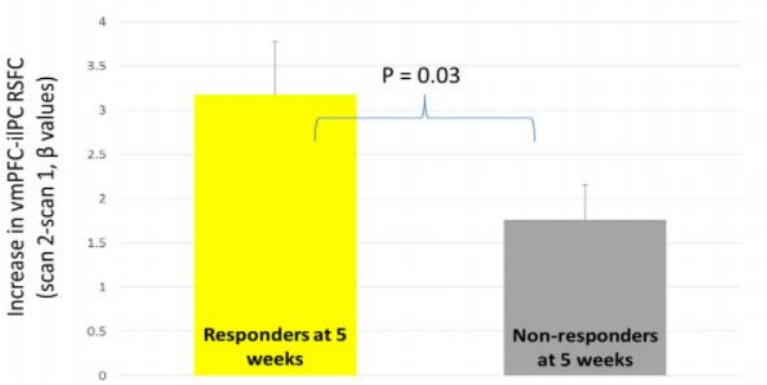

Figure 13: Increased coupling between the vmPFC and the liPC was predictive of clinical response at 5-weeks post- treatment.

Carhart-Harris, R. L., Roseman, L., Bolstridge, M., Demetriou, L., Pannekoek, J. N., Wall, M. B., Tanner, M., Kaelen, M., McGonigle, J., Murphy, K., Leech, R., Curran, H. V., & Nutt, D. J. (2017). Psilocybin for treatment-resistant depression: fMRI-measured brain mechanisms. *Scientific reports*, *7*(1), 13187. https://doi.org/10.1038/s41598-017-13282-7

Also, a decrease in RSFC between the bilateral parahippocampus (PH) and the prefrontal cortex (PFC) was predictive of treatment response at the same endpoint (t=−1.9, p=0.04) – (Figure 14).

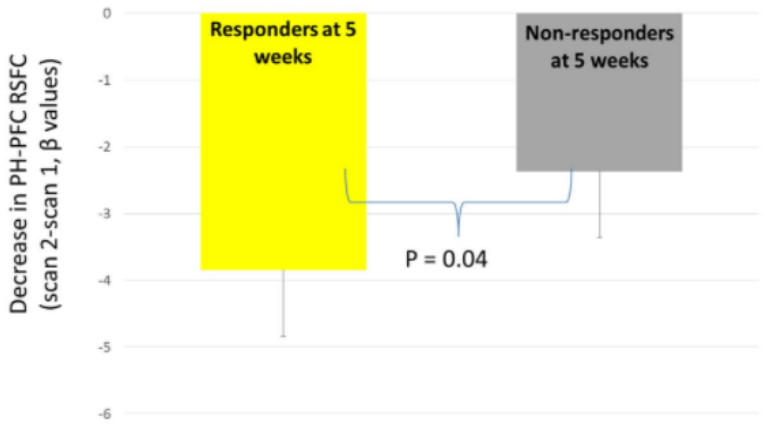

Figure 14: Decreased coupling between the PH and PFC was predictive of clinical response at 5-weeks post-treatment.

Carhart-Harris, R. L., Roseman, L., Bolstridge, M., Demetriou, L., Pannekoek, J. N., Wall, M. B., Tanner, M., Kaelen, M., McGonigle, J., Murphy, K., Leech, R., Curran, H. V., & Nutt, D. J. (2017). Psilocybin for treatment-resistant depression: fMRI-measured brain mechanisms. *Scientific reports*, *7*(1), 13187. https://doi.org/10.1038/s41598-017-13282-7.

Focusing on a rating scale factor related to 'peak' or 'mystical' experience and using scores for the high-dose psilocybin session as a covariate in a parahippocampus RSFC analysis, patients scoring highest on 'peak' or 'mystical' experience had the greatest decreases in PH RSFC in limbic (e.g., bilateral amygdala) and DMN-related cortical regions (e.g. the PCC). analysis. The PH was specifically chosen due to previous work implicating its involvement in related states (Carhart-Harris, Muthukumaraswamy, et al., 2016).

Increased amygdala responses to emotional faces

The amygdala is a subcortical brain structure associated with emotional processing (Sergerie et al., 2008; Janak & Tye et al., 2015) that is involved in the pathophysiology of depression ((Drevets et al., 1992). In depressed patients this structure is hyper-sensitive to negative emotional stimuli and treatment with antidepressants, particularly SSRIs, is known to reduce this (Ma et al., 2015; Godlewska et al., 2012), being a key factor of their therapeutic action (Harmer et al., 2017). Acute treatment with psilocybin in healthy individuals appears to have the same effect (Kraehenmann et al., 2015). Even though there is evidence of psilocybin's effect on the amygdala with healthy volunteers, little is known about this relation in depressed patients. A study involving patients with TRD that underwent psilocybin treatment sessions, sought to investigate the antidepressant effect of psilocybin on amygdala responses to emotional faces (Roseman, Demetriou, et al., 2018).

Patients took a BOLD fMRI Emotional Faces Images Task, where faces with either fearful, happy or neutral expressions were shown to them before and one day after psilocybin treatment. Since psilocybin is correlated with improved mood in the days after the acute experience (Majić et al., 2015; Winkelman et al, 2014), the team predicted that responses to emotional faces in the amygdala would be altered post-treatment and that would be correlated with changes in depressive symptoms. Responses to fearful faces was of special interest, since treatment with SSRIs reduces amygdala responses to negative emotional stimuli (Ma et al, 2015).

The right amygdala showed increased post-treatment responses for fearful ($p=0.001$) and happy ($p=0.022$) expressions. Also, change (10.2±5.3), response (63.2%) and

remission (57.9%) in BDI scores and responses at 1-day (68.4%), 1-week (63.2%) and 3-weeks (63.2%) in QIDS scores were both related to increases in amygdala responses for fearful>neutral faces, with greater activations relating to better outcomes.

Quality of the acute psychedelic experience as a predictor of therapeutic efficacy

One of the key pillars to psychedelic-assisted therapy is that occurrence of a deep and transformative psychological experience is critical to the treatment's efficacy. Evidence has demonstrated that a profound and transformative 'mystical' experience during this therapy can be classified among one of the most meaningful of a person's life, even months after the session occurred (Griffiths et al., 2006; Griffiths et al., 2008). Although the term "mystical" or mystical-type experience can be problematic for the progression of science, due to its relationships with the supernatural (R. L. Carhart-Harris & Goodwin, 2017), we must not forget that only the phenomenology and the measure of the experiences are being highlighted.

A study regarding patients with TRD that went through psilocybin-assisted psychotherapy, focused on whether the quality of the acute experience would predict long-term clinical outcomes (Roseman, Nutt, et al., 2018). To measure the subjective psychedelic experience, the altered state of consciousness questionnaire (ASC) was used (Dittrich et al., 1998), which can be divided into 5 dimensions: *oceanic boundlessness* (OBN), related to the so called 'mystical' experience; *dread of ego dissolution* (DED), where acute anxiety is a key aspect; *visionary restructuralization* (VRS), that measures altered perception and meaning including visual hallucinations and synesthesia; *auditory alterations* (AUA); and *vigilance reduction* (VIR). The questionnaire was completed retrospectively by the patient as the psilocybin session was coming to an end (i.e., ∼5–6 h post ingestion). OBN and DED were used as predictors of therapeutic outcome at 5 weeks. The QIDS-SR score, evaluated at 5 weeks after the psilocybin session, was used as the primary clinical endpoint outcome measure. Furthermore, the authors considered that a specific correlation between OBN and depression changes would be more specific to predict outcomes, than a correlation between VRS and AUA and depression changes.

As hypothesized, high OBN and low DED predicted 54% of the variance of clinical outcomes at 5 weeks ($p = 0.002$ and $p = 0.003$, respectively, for main effects) and, when comparing to VRS and AUA, OBN was more significantly predictive, confirming its specificity ($p < 0.05$). Also, it was also noted that greater DED experiences were correlated to less therapeutic outcomes.

DISCUSSION

In light of previous studies reviewed in this work, psilocybin appears to be safely administered in patients with Depression and TRD, as long as it is done under the right environment. Although the direct pharmacological effect of psilocybin plays an important role in benefiting TRD, the way this treatment is approached (Carhart-Harris, Bolstridge, et al., 2016) may also play a relevant part (Carhart-Harris, Roseman, et al., 2018). The preparation for this treatment should include a careful screening of patients and monitoring during the administration sessions and adequate psychological support before, during and after the sessions (Johnson et al., 2008). Patients seemed to tolerate the acute effects of psilocybin well and no serious adverse effects were reported, consistent with its favorable toxicity profile (Passie et al., 2002; Nichols et al., 2004; Johnson et al., 2008). Also, in line with previous works presented (O'Brien et al, 2006), no craving behaviors or withdrawal symptoms seem to exist with the treatment with psilocybin.

In the studies presented above regarding TRD, psilocybin seems to show a persistent and sustained antidepressant effect, congruent with previous studies regarding treatment with psilocybin for other chronic psychiatric conditions, like MDD (Davis et al., 2021). The response rate to psilocybin was 67% at 1 week after treatment, and seven of these eight patients also met criteria for remission. Moreover, 58% of the patients maintained their response for 3 months, and 42% remained in remission. Examining the follow-up done at 6 months, depressive scores also showed a significant reduction compared to baseline. This seems promising since spontaneous recovery from TRD is rare, and many of the patients reported having depression for most of their lives, since the mean estimated illness duration was 17,8 years (Carhart-Harris, Bolstridge, et al., 2016). Scores related to anhedonia and anxiety were also reduced.

When comparing psilocybin with escitalopram as a treatment for patients with TRD, the depression scores did not differ between both groups at 6 weeks (primary outcome). Although secondary outcomes favored psilocybin over escitalopram, the confidence intervals for the between-group differences were not adjusted for multiple comparisons, so no conclusions can be drawn from these results. However, we can highlight that the patients in the psilocybin group reported greater perceived

improvements in the ability to cry and feel compassion, intense emotion and pleasure and reported feeling less drowsy than those in the escitalopram group. This is consistent with the interviews done 6 months after the high dose of psilocybin, where patients described a shift towards a feeling of reconnection to their senses, themselves, others and the world around them, as well as an acceptance of their emotions (Watts et al., 2017). We can then suggest that the benefit of psilocybin-assisted therapy is not restricted to a reduction in symptoms, but also to a gain in happiness, which has been defined as "pleasure, engagement and meaning" (Seligman et al., 2004).

Patients also reported to the interviewers that former treatments, such as antidepressants or CBT, were felt as reinforcing the disconnection and emotional avoidance of their depression (Watts et al., 2017). In fact, SSRIs are associated with emotional moderation or 'blunting' (Price et al., 2009). For some, these treatments nurtured a view where their psychological pain should be systematically suppressed, rather than explored as a symptom of an underlying problem that needs to be accessed and processed (Watts et al., 2017). On the other hand, with psychedelic-therapy patients assessed more easily to their pain and past traumas. This resonates to a rationale behind the use of mind-revealing drugs like psychedelics with psychotherapy, since they bring suppressed emotions to the surface by dismantling psychological defenses, sometimes with cathartic effect (Eisner et al., 1958; Gasser et al., 2014; Grof et al, 2008; Carhart-Harris, Roseman, et al., 2018).

Accompanying the clinical improvements among patients, changes in personality measures were also found. This is the first time these changes have been reported in patients with depression that underwent treatment with psychedelics, expanding the findings with healthy volunteers (MacLean et al., 2011; Carhart-Harris et al., 2016; McGlothlin and Arnold., 1971; Studerus et al., 2011; Barbosa et al., 2016). The idea that a single dose of a psychedelic can induce lasting changes in personality seems intriguing, thus challenging the assumption that personality traits can only change slowly and are known to be relatively fixed by adulthood (Costa & McCrae, 1997; Mccrae & Costa et al., 1997). For example, longitudinal studies have shown that personality changes after the age of 30 are typically subtle and gradual, that is around 1–2 T-score points per decade, with a subtle drop in *Openness* and *Extraversion* scores and a slight increase *Agreeableness* in older age (Terracciano et al., 2005).

The changes found from pre- to post-treatment seem to be correspondent with observations from a study of patients with major depression that underwent treatment with SSRIs (Costa et al., 2005). More specifically, the same four of the five domains analyzed in both trials - *Neuroticism, Extraversion, Openness* and *Conscientiousness* - changed toward the personality profile of healthy populations (although *Conscientiousness* only at trend-level in the psilocybin study). Also, several of the facet changes overlapped in the two studies. Decreases in the *Neuroticism* facet, a vulnerability marker for affective disorders (Duggan et al., 1995), and increases in *Extraversion*, a facet associated with general positive affect (Watson & Naragon-Gainey et al., 2014), have previously been found to be significantly correlated with SSRI/s and SRNIs reduction of depression severity (Bagby et al., 1999). In accord with this, decreases in depressive symptoms with psilocybin were associated with decreases in *Neuroticism* and increases in *Extraversion*, although only to a trend-level, with no significant correlation. In contrast, increased *Openness* did not correlate with treatment response and neither was it different between responders and non-responders. Also, none of the *Openness* facets were found to be significantly changed after successful antidepressant treatment in the study by Costa et al. In contrast, the facets *Openness to actions* and *to values* significantly increased in the psilocybin study. *Openness to actions* relates to not being set in one's way, and on the other hand, being ready to try and do new things (Erritzoe et al., 2018). *Openness to values* means valuing permissiveness, open-mindedness, and tolerance (Erritzoe et al., 2018). These two facets therefore seem to reflect an active approach on the part of the individual to try new ways of doing things and consider other peoples' values and/or worldviews. This seems to be concordant with the patients reports in the 6-months follow-up interviews (Watts et al., 2017). Thus, the modification of *Openness* and its facets following psilocybin treatment might be an outcome separate and additional to the changes that have previously been seen with antidepressant treatment (Roberts et al., 2017).

The effects of psilocybin on the pessimism bias of patients with TRD are also worthy of discussion. Patients with depression often see themselves and the world around with an unyielding pessimism (Styron et al., 1992). Their cognition may be too fixed and therefore they lose their ability to think and behave in a flexible and normal way. An explanation for this may be a decrease in metastability where a introspective default-

mode dominates cognition (Carhart-Harris et al., 2014). The aggressive self-critical focus that accompanies a loss or abandonment of object-cathexis in depression quite naturally leads to suicidal thoughts and acts (Carhart-Harris et al., 2008). Therefore, narrow-mindedness is to pessimism what openness (MacLean et al., 2011) is to optimism and strategies that promote the latter may be effective treatments for depression (MacLean et al., 2011).

Before the treatment with psilocybin, patients with TRD showed a pessimism bias when predicting the probability of life events occurring (Lyons & Carhart-Harris et al., 2018), as the cognitive-bias model of depression concluded (Beck et al., 1967, 1976). Also, the pessimism had a significant correlation with the depressive symptoms of patients, consistent with the depressive bias hypothesis, stating that as depressive symptoms increase in severity, judgments become more negatively biased (Beck et al., 1976). After the treatment, patients' pessimism bias decreased to control levels, showing no longer any cognitive bias. Depressive symptoms also decreased and both variables demonstrated a positive correlation. Previous studies also have shown increases in optimism following psilocybin-assisted therapy in patients suffering cancer related depression and anxiety (Grob et al., 2011; Griffiths et al., 2016; Ross et al., 2016). Also, long-lasting improvements in optimism have also been observed in healthy volunteers following a single dose of a psychedelic (MacLean et al., 2011; Carhart-Harris et al., 2016) and there is also evidence that recreational psychedelic users are more optimistic (or less pessimistic) than non-users (Grob et al., 1996). Psychedelic compounds have previously been shown to increase positive mood (Kraehenmann et al., 2015; Schmid et al., 2015) and often induce lasting changes in attitudes and behavior associated with a more positive outlook (McGlothlin and Arnold et al., 1971; Griffiths et al., 2006, 2008; Studerus et al., 2011). Patients predicted significantly more desirable events post-treatment and made more accurate predictions that better reflected their actual life situation (Lyons & Carhart-Harris et al., 2018). To this day, this is the first study that has used an objective behavioral instrument to address the cognitive bias related with depression and how it changes after treatment with a psychedelic. These findings suggest that psilocybin, when administered with psychological support in a controlled environment, may alleviate the pessimism bias present in depression, enabling patients to have a more clear and accurate perspective of their future.

As presented above, SSRIs reduce the responses to negative emotional stimuli in the amygdala (Ma et al., 2015; Godlewska et al., 2012), and this is a key element of their therapeutic effect (Harmer et al., 2017). Furthermore, psilocybin appears to have the same effect in healthy individuals (Kraehenmannet al., 2015). Unspecific decreases in the right amygdala responses to negative and neutral stimuli (not faces) were assessed during the acute effect of psilocybin. However, increased amygdala responses to emotional faces were found after treatment with psilocybin (Roseman et al., 2017). The post-treatment increases in responses to fearful faces versus neutral were significantly related to better clinical outcomes. Caution with this interpretation is needed since the post-acute changes in brain function are very different if not antithetical to the acute effect of psilocybin (Carhart-Harris et al., 2017). In addition, psilocybin appears to improve processing of emotional faces in TRD, and this correlates with reduced anhedonia scores post-treatment (Stroud et al., 2018). This is a major component of depression that is unresponsive to standard antidepressant treatments (Lally et al., 2014). Both psilocybin, with psychological support, and ketamine (Lally et al., 2014) appear to facilitate an immediate improvement in anhedonia in depression.

The findings of increased amygdala responsiveness and improvements in the processing of emotional faces post-treatment with psilocybin seem to be consistent with the patients' descriptions of feelings of reconnection and acceptance after the treatment with psilocybin (Watts et al., 2017) and suggest a different neurobiological basis to the alleviation of depressive symptoms from that of SSRIs. From a neurochemical and neurobiological level, it has been suggested that while SSRIs act primarily on the postsynaptic 5-HT1A receptor, promoting a passive coping (i.e., tolerating a source of stress) pathway which improves stress tolerability, psilocybin promotes an active coping (i.e. actively addressing a source of stress) pathway associated with heightened plasticity, which, with the right support, can improve one's ability to identify and overcome sources of stress by changing outlook and/or behavior (Carhart-Harris & Nutt et al., 2017) – (Figure 15).

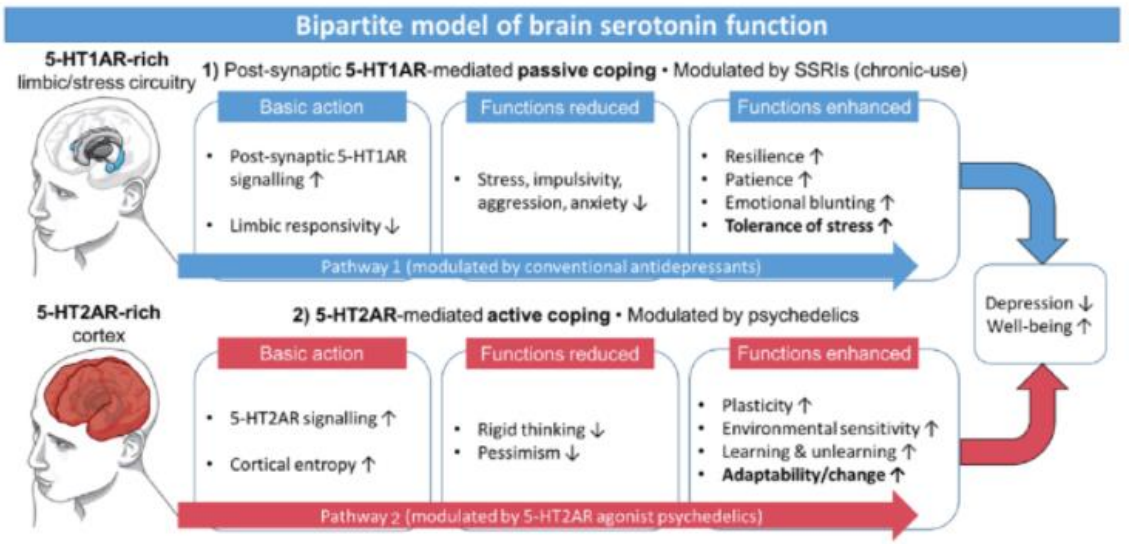

Figure 15: A two-part or 'bipartite' model of brain serotonin function.

Carhart-Harris, R. L., & Nutt, D. J. (2017). Serotonin and brain function: a tale of two receptors. *Journal of psychopharmacology (Oxford, England)*, *31*(9), 1091–1120. https://doi.org/10.1177/0269881117725915.

This bipartite model seems to explain how different drugs (SSRIs and psychedelics) modulate the serotonergic system in different ways, achieving complementary adaptive and potentially therapeutic outcomes. However, these findings require further work to test their replicability and whether enhanced amygdala responsiveness is associated with the enduring positive effects of psychedelics.

Besides the fact that psychedelics and SSRIs act via different pathways, we need to understand that they cannot easily be taken in combination, since conventional antidepressants seem to attenuate the characteristic psychological effects of psychedelics (Bonson et al., 1996). Therefore, psychedelics must not be seen as a magic bullet treatment nor as a competition to traditional treatments, but rather, as a catalyst or a supplement of these treatments. For example, in a recent trial regarding tobacco addiction, a psilocybin dosed session introduced at a strategic point within a standard 12-week course of CBT, with the intention of improving insight and motivation, showed considerable success (Johnson et al., 2017).

Another topic demanding discussion is the neurobiological mechanism through which psychedelics work. As stated above, diminished functional activity in certain regions within the DMN, that are over-engaged in depression (Greicius et al., 2007; Berman et al., 2011), has been observed under the acute effects of psilocybin (Carhart-Harris et al.,

2012). Also, increased activity within this network seems to be a key factor in depressive moods, specifically rumination (Berman et al., 2011; Zhou et al, 2020) as well as neuroticism (Adelstein et al., 2011). Following this train of thought, the findings observed one day post treatment with psilocybin in patients with TRD are intriguing, since the post-treatment within-DMN vm-PFC-ilPC increased integrity predicted treatment response at 5 weeks (Carhart-Harris et al., 2017). However, these findings are consistent with studies done with ECT as an option treatment for depression (Mulders et al., 2016), where a decreased integrity in the DMN is observed in the acute state and increased, or normalized, afterwards, followed by improvements in depressive symptoms.

Psychedelics are known to cause disruption at multiple levels in the brain. At the neurochemical and neurophysiological level, through a 5-HT2AR signaling in the neocortical layer 5 pyramidal neurons, they induce an asynchronous mode of glutamate release (Larkum et al., 2009) and a spike-to-field decoherence (Celada et al., 2008). This irregular excitation is likely to be responsible for the dysregulation appearing at a broader level in certain areas of the DMN, for example in terms of decreased oscillatory power across a broad range of frequency bands (Muthukumaraswamy et al., 2013). Furthermore, prominent cortical rhythms such as those in the alpha and beta frequency bands are known to be involved in certain predictions, expectations or beliefs (Mayer et al., 2016); Fries et al., 2015). Also, psychedelics seem to act in high-level intrinsic networks like the DMN (Carhart-Harris, Muthukumaraswamy, et al., 2016), by compromising its 'resting-state' or 'intrinsic' integrity, as has these networks' functional segregation (Carhart-Harris et al, 2016; Roseman et al., 2014; Müller et al., 2018). This is consistent with the principle that psychedelics induce a transient disintegration and desegregation of intrinsic brain integration (Tagliazucchi et al., 2016; Petri et al., 2014) – (Figure 16).

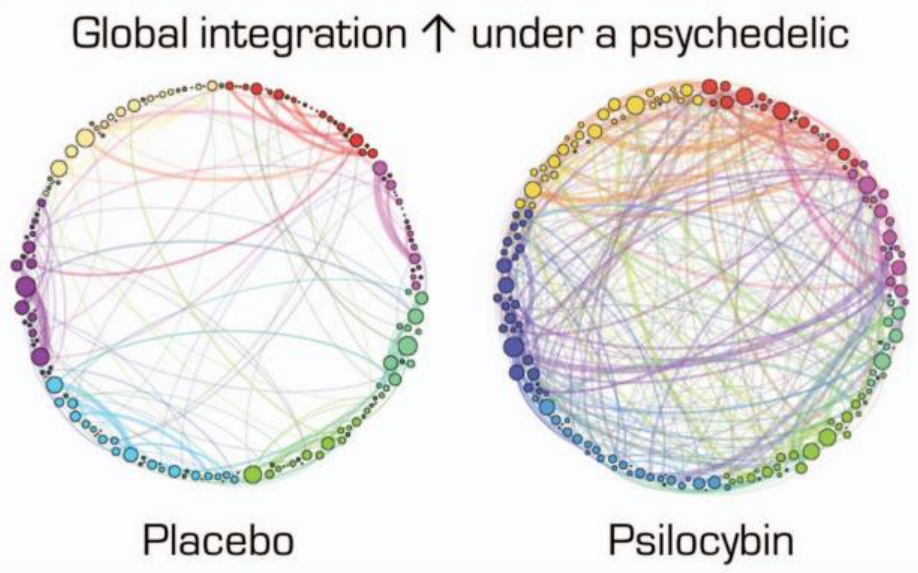

Figure 16: Global integration in placebo (a) and under the influence of psychedelics (b)

Petri, G., Expert, P., Turkheimer, F., Carhart-Harris, R., Nutt, D., Hellyer, P. J., & Vaccarino, F. (2014). Homological scaffolds of brain functional networks. *Journal of the Royal Society, Interface*, *11*(101), 20140873. https://doi.org/10.1098/rsif.2014.0873.

Considering this disruption process caused by psychedelics as well as the results found in the f-MRI study with patients suffering from TRD (Carhart-Harris et al., 2017), what seems to happen is a "reset" mechanism where acute modular disintegration (in the DMN) leads to a subsequent re-integration and resumption of normal functioning. In other words, the DMN integrity is decreased acutely and increased (or normalised) post-acutely. In fact, in their six-month follow-up interviews, patients described a sudden dramatic change in the quality of their consciousness, like a sense of mental freedom, as if their minds were opened up or "rebooted" (Watts et al., 2017). This seems to be consistent with previous works regarding psychedelics, since, through the stimulation of the 5-HT2AR, they increase psychological and cognitive flexibility (Kuypers et al., 2016; Carhart-Harris and Nutt et al., 2017) and make the brain enter a state of plasticity that enhances learning and change (Carhart-Harris, Erritzoe, et al., 2012; Carhart-Harris, Kaelen, et al., 2016; Carhart-Harris, Muthukumaraswamy, et al., 2016; Brouwer et al, 2021). Such a process can be likened to annealing in metallurgy, where a metal is heated in order to make it malleable. In this case, the metal is analogous to the mind and brain

and the heat is the excitatory action of the psychedelic (Watts et al., 2017). In fact, certain studies indicate that brain entropy, that has been identified as a key feature of the psychedelic state (Carhart-Harris et al., 2014), is consistent with the brain being near a point of "criticality" (Atasoy et al., 2017), where a system resides in a functional "sweet spot", placed between order and disorder, where it retains information appropriately (by being sufficiently ordered) and adapts and becomes sensitive to change (by being sufficiently disordered). Therefore, psychedelics seem to work by dismantling reinforced patterns of negative thought and behavior by breaking down the stable patterns of brain activity upon which they rest (Carhart-Harris et al, 2014).

Another interesting finding is the decreased CBF found specifically in the left amygdala and its correlation with reduced depressive symptoms (Carhart-Harris et al., 2017). This could be seen as a remediated effect caused by psilocybin, given similar reports with ECT (Bolwig, 2014) and previous findings of elevated resting-state amygdala CBF and metabolism in mood disorders (Drevets et al., 1992; Coombs et al., 2014; Abercrombie et al 1998). Moreover, the same trial found that a decrease in RSFC between the bilateral parahippocampus (PH) and the prefrontal cortex (PFC) was predictive of response to treatment with psilocybin at 5 weeks, that has generally been found to be elevated in depression (Kaiser et al., 2016). Furthermore, patients scoring highest in the rating scale factor related to "peak" or "mystical" experience, experienced the greatest decreases in PH RSFC in limbic (e.g., bilateral amygdala) and DMN-related cortical regions (e.g., the PCC). This confirms the premise from previous work indicating that the post-acute brain changes are mediated by the quality of the acute experience under psychedelics (Griffiths et al., 2011; Griffiths et al., 2016; Ross et al., 2016). From a whole-brain systems level, the increased cortical entropy feature of the psychedelic experience (Carhart-Harris et al., 2014), is related to high-level subjective experiences like "ego-dissolution" (Nour et al., 2016; Atasoy et al., 2017; Schartner et al., 2017) that are important to the mystical-type experience. When analyzing the study that sought to investigate if the quality of the acute psychedelic experience would predict long-term clinical outcomes in patients with TRD (Roseman et al., 2018), high OBN (a dimension related to the mystical-type experience) and low DED (a dimension related to anxiety) were predicted of more positive long-term clinical outcomes. This comes in line with previous findings showing that psychedelic-induced peak or mystical-type experiences

are predictive of positive long-term outcomes (O'Reilly and Funk, 1964; Klavetter & Mogar et al., 1967; Richards et al., 1977; Maclean et al., 2011; Bogenschutz et al., 2015; Griffiths et al., 2016; Johnson et al., 2016; Ross et al., 2016). Furthermore, the correlation between OBN and changes in depression symptoms predicted outcomes more specifically than a correlation between VRS (vigilance reduction) and AUA (auditory alterations) and the same changes. This infers that the therapeutic properties of psilocybin do not come only from its pharmacological action, but are also experience dependent. Furthermore, low DED combined with high OBN predicted 54% of the variance of clinical outcomes at 5 weeks, emphasizing the premise that minimizing anxiety and relinquishing psychological resistance is extremely important in psychedelic therapy (Eisner and Cohen et al., 1958; Grof et al., 2008), as well as the careful attention that needs to be given to the context and environment on which these experiences happen ((Hartogsohn, 2017); Carhart-Harris, Roseman, et al., 2018; Brouwer & Carhart-Harris et al., 2021). Understanding the neurobiological mechanisms of the 'mystical' or peak experiences should enable us to better understand, define and study them. This becomes important since they are a key factor in the success of psychedelic therapy.

As stated above, psychedelic-assisted therapy lays its grounds in three major steps: Preparation, the Psychedelic Session and Integration (Johnson et al., 2008). Again, preparation is fundamental for maximizing the potential of the psychedelic session and integration is crucial for processing the messages from the psychedelic session and introducing them into the daily life. In the qualitative data obtained from the open-label study (Watts et al., 2017), a process of movement from disconnection to connection and from emotional avoidance to acceptance was observed, suggesting that increased psychological flexibility is an important factor through which psychedelics can be beneficial. In fact, improvements in psychological flexibility during therapy predict positive outcomes (Vowles et al., 2014). Based on the psychological flexibility model (PFM) (Hayes et al., 2012) that outlies six flexibility processes (contact with present moment, acceptance, cognitive defusion, self as context, committed action and values*)* and considering the themes of "acceptance" and "connection" as keys of the psychedelic experience (Watts et al., 2017), a new model has been proposed to guide psychedelic preparation and integration (Watts & Luoma et al., 2020) – (Figure 17). This new model, the ACE (Accept, Connect and Embody) model restructures the previous six

psychological flexibility processes in an acceptance triad (defusion, present moment focus and willingness) and a connection triad (self as context, values and committed action).

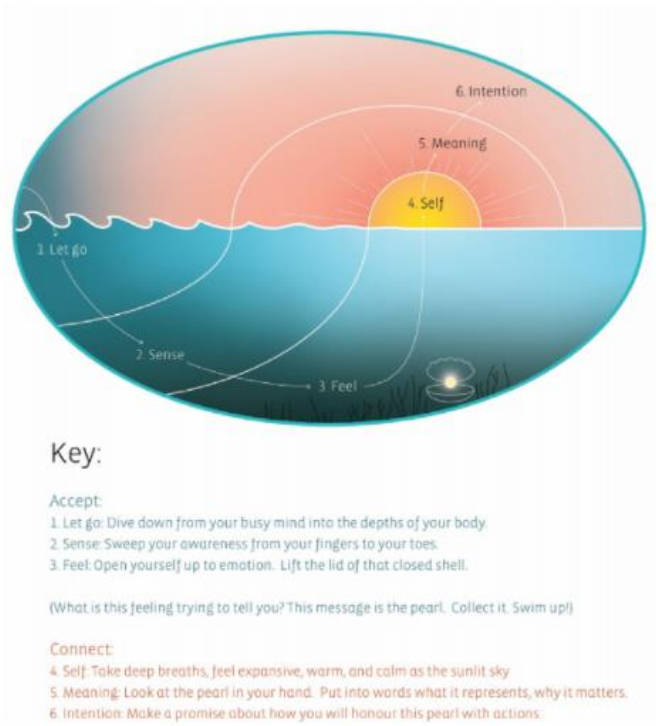

Figure 17: The ACE map.

Watts, R., & Luoma, J. B. (2020). The use of the psychological flexibility model to support psychedelic assisted therapy. In Journal of Contextual Behavioral Science (Vol. 15, pp. 92–102). Elsevier Inc. https://doi.org/10.1016/j.jcbs.2019.12.004.

This model infers that both acceptance (of uncomfortable experiences) and connecting (to meaning, values and insight) are important. In other words, pain and values are “two sides of the same coin”. This is important because patients with depression tend to live in a state of numb despair and the psychedelic session often bring positive and negative repressed emotions. The Accept (blue) is about accepting moment to moment somatic and emotional experience and opening up to what is painful. The Connect (pink) is about connecting to the meaningful, beautiful and transcendent. The Embodiment runs all the way through and refers to the way the other two triads occur in a whole-body process of sensing, feeling and thinking. This model is a travel to psychedelic therapy and life in general. It serves as a framework for therapists to guide patients during preparation and integration sessions as well as home practice.

LIMITATIONS

Although psychedelic therapy with psilocybin seems promising as a treatment for TRD, we must not forget to point out the limitations coming from early trials. The pilot study where most of the variables where assessed (Carhart-Harris et al, 2016) had an open-label design and lacked a control condition. Also, most of the patients were male, thus limiting extrapolation to the general population since depression rates are found to be higher in males than females (Kubitz et al., 2013). Moreover, the sample size was small and although all patients showed some reduction in their depressive symptoms, since suggestibility is known to be enhanced by psychedelics, leading to more positive outcomes (Carhart-Harris et al., 2015), this could also be related to expectation from the recruited patients, so strong inferences cannot be made about the treatment's efficacy. In addition to this expectancy bias, a self-referring or self-selection bias was also involved. Most patients in the trial actively sought out the treatment with psilocybin since they believed they wanted to demonstrate that it could and would be effective for them. All of them had TRD, and therefore held a negative view on previous treatments and saw in psilocybin-assisted treatment a positive light. Future double-blind randomized controlled trials could address the role of expectancy and suggestibility by measuring and controlling these variables. However, we need to consider that if expectancy or suggestibility are found to be influential in the context of psychedelic therapy, they could be treated as exploitable components of the treatment model rather than confounding variables. The psychological effects of psychedelics are context-dependent (Carhart-Harris, Roseman, et al., 2018; Brouwer & Carhart-Harris et al, 2021), meaning that perceptions and memories of a person, alongside with the degree to which the environment is supportive at the time of administration influences the content and subjective quality of the psychedelic experience.

Even though a phase 2, double-blind, randomized, controlled trial comparing psilocybin treatment with a SSRI (escitalopram) has been carried out (Carhart-Harris et al, 2021), several limitations were also observed. The efficacy of the treatment with escitalopram would be better if its duration would have been extended for more than 6 weeks, since this drug has a delayed therapeutic action on depression (Trivedi et al., 2006). Although secondary outcomes favored psilocybin, the confidence intervals for the between-group

differences were not adjusted for multiple comparisons, so no conclusions can be made. Efforts were made to recruit more patients by external referrals. However, most of the volunteers were self-referred, and many expressed a preference for the psilocybin treatment, once more creating a selection bias. Again, patients in the trial were not from diverse ethnic and socioeconomic backgrounds and average symptom severity scores at baseline were in the range for moderate depression, thus limiting extrapolations to patients with severe depressive symptoms or treatment-resistant depression.

The early trials presented in this review serve as a prelude to larger randomized clinical trials regarding psilocybin as a treatment for TRD.

CONCLUSIONS

This review aimed to review the current evidence regarding psilocybin-assisted therapy as a treatment option for TRD.

Psilocybin administration, with adequate safeguards (e.g., careful screening and monitoring, alongside with adequate therapeutic support), appears to be a safe treatment option for patients with TRD. This seems to have potential, since a substantial decrease in depressive symptoms after one single dose persisted for at least 6 months in patients with a long duration of their illness. Moreover, its benefits may not be only related to a reduction in symptoms, but to broader effects like changes in personality, perspectives, behaviors, and psychological wellbeing overall. Therapy with psilocybin seems to overlap SSRIS effects in some patients regarding reduction of depressive symptoms. The two treatments seem to act through different pathways, modulating the serotonergic system via a bipartite module. Therefore, psilocybin must not be seen as a substitution to the modern treatments for depression, but rather as a complement. From a neurobiological level, a "reset" mechanism is proposed on the DMN. The acute effect of psilocybin seems to create a modular disintegration in the DMN, producing an "entropic" brain state that through neuroplasticity is capable of learning and change. After the acute effect, re-integration and resumption of normal functioning is followed. This increased entropy seems to be correlated with the mystical-type experience produced by psychedelics, whose quality appears to be important to the long-changes in depressive symptoms. Also, a therapeutic model of exploration, acceptance and integration of painful experiences is presented.

Research and funding to better understand the potential treatment of psilocybin-assisted therapy still lacks support from drug regulatory agencies. This fact is understandable when considering the complex social background surrounding classic psychedelics, especially if we refer to the counterculture that took place in the 1960s and 1970s. Nevertheless, since evidence of their safety and efficacy is growing with the example of the studies presented, it appears to be crucial for these agencies to take a supporting role in the future research regarding psychedelic therapy, particularly for TRD.

ACKNOWLEDGMENTS

To everyone, friends and family, that crossed my path and made me the person that I am today. Thank you for all the love, friendship and compassion you gave and continue to give, making me want to become a better version of myself.

Before I enjoyed nature, now I feel part of it.

Before I was looking at it as a

thing, like TV or a painting.

You're part of it, there's no separation or distinction,

you are it.

Patient 1 from the 2016 open-label trial

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