Hallucinogenic/psychedelic 5HT2A receptor agonists as rapid antidepressant therapeutics: Evidence and mechanisms of action

Rafael Guimarães dos Santos1,2, Jaime EC Hallak1,2,3, Glen Baker2,3 and Serdar Dursun2,3

Abstract
Major depressive disorder (MDD) is among the most prevalent mental health disorders worldwide, and it is associated with a reduced quality of life and enormous costs to health care systems. Available drug treatments show low-to-moderate response in most patients, with almost a third of patients being non-responders (treatment-resistant). Furthermore, most currently available medications need several weeks to achieve therapeutic effects, and the long-term use of these drugs is often associated with significant unwanted side effects and resultant reductions in treatment compliance. Therefore, more effective, safer, and faster-acting antidepressants with enduring effects are needed. Together with ketamine, psychedelics (or classic or serotonergic hallucinogens) such as lysergic acid diethylamide (LSD), psilocybin, and ayahuasca are among the few compounds with recent human evidence of fast-acting antidepressant effects. Several studies in the 1950s to 1970s reported antidepressive and anxiolytic effects of these drugs, which are being confirmed by modern trials (LSD, one trial; psilocybin, five trials; ayahuasca, two trials). The effects of these drugs appear to be produced primarily by their agonism at serotonin (5-hydroxytryptamine, 5-HT) receptors, especially the 5-HT2A receptor. Considering the overall burden of MDD and the necessity of new therapeutic options, the promising (but currently limited) evidence of safety and efficacy of psychedelics has encouraged the scientific community to explore more fully their beneficial effects in MDD.

Keywords
Hallucinogens, psychedelics, 5-HT2A receptor, major depressive disorder

Background
Major depressive disorder (MDD) is highly prevalent in the population and is one of the main causes of disability worldwide; it is also associated with increased suicidality and enormous costs to health care systems (Blackburn, 2019; Brådvik, 2018; Penn et al., 2012). The monoamine theory suggests that reductions in functional availability of the monoamines norepinephrine and/or 5-hydroxytryptamine (5-HT, serotonin) in certain areas of the brain are associated with depression, and that drugs that increase that functional availability will improve depressive symptomatology. Although the monoamine theory was important in the development of many of the antidepressant drugs currently available, it became obvious that it did not explain several aspects of the etiology of depression. In addition, the medications based on this theory often need several weeks to achieve therapeutic effects, result in only moderate rates of response and remission, and often produce unwanted side effects. Therefore, innovative treatments with different mechanisms of action and rapid and enduring effects are needed (Blackburn, 2019; Duman, 2014; Penn et al., 2012).

The description of the fast-acting and enduring antidepressant effects of the N-methyl-D-aspartate (NMDA) glutamate receptor antagonist ketamine in 2000 (Berman et al., 2000) is considered a major advance in understanding the etiology and treatment of mood disorders, which for many years were based mostly on the monoaminergic imbalance theory. The evidence of fast-acting and enduring antidepressant effects of ketamine opened the doors to innovative approaches to treat depression by the modulation of other neurotransmission systems. Unfortunately, ketamine has psychotomimetic properties, abuse potential, and possible bladder toxicity, limiting its prolonged use if not administered properly (Jauhar and Morrison, 2019). Other drugs with fast-acting antidepressant effects are the psychedelics (or classic or serotoninergic hallucinogens) such as lysergic acid diethylamide (LSD), psilocybin (present in several mushroom species), and ayahuasca (N,N-dimethyltryptamine (DMT)- and β-carboline-containing concoction used in Amazonian medicine). Evidence for these effects and possible mechanisms are discussed below.

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Evidence for psychedelics as fast-acting antidepressants

Receptor-level evidence

Serotonergic psychedelics have been reported to produce profound modifications in affect, perceptions, and cognition. These drugs share a common mechanism of action involving agonism at cortical 5-HT1A/2A/2C receptors (Halberstadt, 2015; López-Giménez and González-Maeso, 2018; Marek, 2018; Nichols, 2004, 2016). Several receptor-level and molecular studies have shown that 5-HT1A/2C receptors play a role in the effects of psychedelics (Halberstadt, 2015; Marek, 2018; Nichols, 2004, 2016). However, the 5-HT2A receptor seems to be the main receptor activated by psychedelics (López-Giménez and González-Maeso, 2018; Nichols, 2004, 2016). For instance, this receptor activates different signaling transduction pathways from those activated by 5-HT1A/2C receptors (Berg et al., 1998; López-Giménez and González-Maeso, 2018). Further, 5HT2A receptors are mostly condensed in the choroid plexus (Palacios et al., 2017), while 5-HT2A receptors are densely expressed in the prefrontal cortex (PFC), anterior (ACC) and posterior (PCC) cingulate cortices, hippocampus, and the amygdala (dos Santos and Hallak, 2020; dos Santos et al., 2016; Nichols, 2004, 2016; Nutt et al., 2020). Activation of the 5-HT2A receptor in these regions induces glutamate release and stimulates c-fos expression in the PFC and ACC and increases brain-derived neurotrophic factor (BDNF) expression in the PFC (López-Giménez and González-Maeso, 2018; Marek, 2018; Nichols, 2004, 2016). Activation of the 5-HT2A receptor by LSD and DMT increases dendritic arbor complexity, promotes dendritic spine growth, and stimulates synapse formation (Ly et al., 2018). Interestingly, a recent study involving experiments in vitro and in vivo showed that DMT promoted the generation of new neurons in the mouse hippocampus by a mechanism involving signaling via the sigma-1 receptor (S1R) (Morales-Garcia et al., 2020).

Evidence from animal models

Preclinical evidence shows that 5-HT2A receptor agonists have antidepressant effects. Antidepressant-like actions were reported in rodents after administration of the 5-HT2A agonist 2,5-dimethoxy-4-iodoamphetamine (DOI) (Masuda and Sugiyama, 2000), LSD (Buchhorn et al., 2014; Hibicke et al., 2020), psilocybin (Hibicke et al., 2020), and DMT (Cameron et al., 2018, 2019). However, a rodent study with psilocin and psilocybin showed no antidepressant effects (Jøfse et al., 2019). This negative result could be explained by the fact that the rat strain used in this study (Flinders Sensitive Line rats) has extremely low central 5HT2A mRNA expression (Hibicke et al., 2020). A recent study showed that a single dose of the DMT-rich botanical preparation ayahuasca (which also contains monamine oxidase-inhibiting β-carboline) which reduce the catalebic breakdown of DMT induced fast (24h) and prolonged (14 days) antidepressant effects in a juvenile primate model of depression (da Silva et al., 2019).

Evidence from human studies

Until their prohibition in the late 1960s/early 1970s, LSD, psilocybin, and mescaline were investigated in humans for the possible treatment of mood, anxiety, and substance use disorders (for reviews see: dos Santos and Hallak, 2020; McGlothlin and Arnold, 1971; Nichols, 2014, 2016; Nutt et al., 2020; Riedlinger and Riedlinger, 1994). Recent systematic reviews of studies in depression (Rucker et al., 2016), anxiety (Weston et al., 2020), substance use disorders (Krebs and Johansen, 2012), and in depression and anxiety associated with life-threatening diseases and cancer (Reiche et al., 2018) reported promising results from these early trials. Improvements often included fast and enduring symptom reduction (Krebs and Johansen, 2012; Reiche et al., 2018; Rucker et al., 2016; Weston et al., 2020). However, these previous studies often had methodological shortcomings, including broad definition of diagnoses, non-standardized procedures, varying drug doses, and lack of placebo and controls. Moreover, the experimental paradigms were very heterogeneous. Two of the most used therapeutic models were the psycholytic and the psychedelic. In the psycholytic model low/moderate doses of psychedelics were administered on multiple occasions, usually in a psychoanalytic approach. The psychedelic model used single/few high doses to induce “peak” or “mystical” experiences (Grinspoon and Bakalar, 1979). However, some hybrid models were also used in which the psycholytic and psychedelic approaches were used together or in which psychedelics were combined with hypnosis (hypnodelic treatment technique) (Grinspoon and Bakalar, 1979; Lemercier and Terhune, 2018; McGlothlin and Arnold, 1971; Nichols, 2014, 2016; Riedlinger and Riedlinger, 1994).

More recently, controlled trials using LSD (Gasser et al., 2014; n = 12) or psilocybin (Griffiths et al., 2016; Grob et al., 2011; Ross et al., 2016; total n = 92) reported fast (days) and enduring (weeks to months) improvements of depression and anxiety symptoms in patients with life-threatening diseases/cancer. Regarding MDD, a controlled trial with healthy experienced ritual ayahuasca users showed that a single ayahuasca dose acutely (1h post-intake) reduced hopelessness and panic-like symptoms (dos Santos et al., 2007). In an open-label trial with 17 patients with treatment-resistant depression (TRD), a single ayahuasca dose produced fast-acting (hours) and enduring (21 days) reductions in anxiety and depressive symptoms (Sanches et al., 2016). This result was recently replicated in a randomized trial with 29 patients with TRD, where a single ayahuasca dose reduced depressive and anxious symptoms compared to placebo from the first day until 1 week afterwards (Palhano-Fontes et al., 2019). It should be noted that most patients in this sample (76%) had a comorbid personality disorder, which could have influenced the results since patients with comorbid personality disorders can present higher placebo responses (Palhano-Fontes et al., 2019). In all three trials ayahuasca was well tolerated: no serious adverse events were reported, with transient vomiting and nausea as the more common adverse effects.

In the case of psilocybin, an open-label trial with 12 volunteers with TRD reported that two oral doses of psilocybin (7 days apart) produced rapid (1 week) and sustained (3 months) decreases in depression and anxiety symptoms (Carhart-Harris et al., 2016). These results were recently corroborated by a randomized, waiting list-controlled trial with 24 patients with MDD who received two oral doses of psilocybin (mean of 1.6 weeks apart) (Davis et al., 2020). Psilocybin was well tolerated in both trials: no serious adverse events were reported, with transient anxiety, confusion, headache, and nausea as the more common adverse effects. Although promising, these were open-label trials, and these results need to be replicated in placebo-controlled randomized trials. Indeed, several randomized trials are now underway (for example: NCT03775200, NCT03866174). Information about the above-mentioned trials in clinical populations is presented in Table 1.
Table 1. Summary of the antidepressant and anxiolytic effects of psychedelics in recent trials with clinical populations with depression and anxiety symptoms.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study sample/design</th>
<th>Main results</th>
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</thead>
<tbody>
<tr>
<td>Grob et al., 2011</td>
<td>United States, randomized, double-blind, placebo-controlled, cross-over</td>
<td>Significant reductions in depression (BDI) at the 6-month follow-up compared to placebo ($P &lt; .05$)</td>
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<td>12 patients with anxiety and depressive disorders associated with advanced-stage cancer received psychological support (without psychotherapy) and a single dose of psilocybin (0.2 mg/kg) or an active placebo (niacin, 250 mg)</td>
<td>Significant reductions in anxiety (STAI) at the 1- and 3-month follow-ups compared to placebo ($P &lt; .05$)</td>
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<td>Psilocybin was well tolerated</td>
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<td>Gasser et al., 2014</td>
<td>Switzerland, randomized, double-blind, placebo-controlled, cross-over</td>
<td>Significant reductions in anxiety (STAI) at the 2-month follow-up compared to placebo ($P &lt; .05$)</td>
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<td>12 patients with anxiety and depression associated with life-threatening diseases (e.g., cancer, Bechterew’s disease, Parkinson’s disease, celiac disease) received psychological support/psychotherapy associated with a single dose of 200 µg (experimental dose, $n=8$) or 20 µg (active placebo, $n=4$) of LSD</td>
<td>LSD was well tolerated</td>
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<tr>
<td>Carhart-Harris et al., 2016</td>
<td>United Kingdom, open-label</td>
<td>Significant reductions in depression (QIDS, BDI, HAMD, MADRS) between the 1-week and 3-month follow-ups ($P &lt; .05$)</td>
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<td>12 patients with treatment-resistant MD received psychological support (without psychotherapy) and two psilocybin doses (10 and then 25 mg 7 days apart)</td>
<td>Significant reductions in anxiety (STAI, HADS) at the 1-day and 2-, 6-, 7-, and 26-week follow-ups ($P &lt; .05$)</td>
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<td></td>
<td>Psilocybin was well tolerated</td>
</tr>
<tr>
<td>Griffiths et al., 2016</td>
<td>United States, randomized, double-blind, placebo-controlled, cross-over</td>
<td>Significant reductions in depression (BDI, GRID, HADS, POMS, BSI) at the 5-week and 6-month follow-ups compared to placebo ($P &lt; .05$); difference between doses: $P &lt; .05$</td>
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<td>51 patients suffering from anxiety and depression associated with life-threatening cancer received psychological support/psychotherapy and a high (22–30 mg/70 kg) or low (1–3 mg/70 kg) psilocybin dose</td>
<td>Significant reductions in anxiety (STAI, HADS, HAM-A, BSI) at the 5-week and 6-month follow-ups compared to placebo ($P &lt; .05$); difference between doses: $P &lt; .05$</td>
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<td>Psilocybin was well tolerated</td>
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<tr>
<td>Ross et al., 2016</td>
<td>United States, randomized, double-blind, placebo-controlled, cross-over</td>
<td>Significant reductions in depression (BDI, HADS) at the 1-day and 2-, 6-, 7-and 26-week follow-ups compared to placebo ($P &lt; .05$)</td>
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<td>29 patients with anxiety and depression associated with life-threatening cancer received psychological support with a high dose of psilocybin (0.3 mg/kg) and were compared to psychological support/psychotherapy and niacin (active placebo, 250 mg)</td>
<td>Significant reductions in anxiety (STAI, HADS, HAM-A, BSI) at the 1-day and 2-, 6-, 7-and 26-week follow-ups compared to placebo ($P &lt; .05$)</td>
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<td>Psilocybin was well tolerated</td>
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<td>Sanches et al., 2016</td>
<td>Brazil, open-label</td>
<td>Significant reductions in depression (HAM-D, MADRS) from 40 to 180 minutes and at the 1-day and 1-, 2-, and 3-week follow-ups ($P &lt; .05$)</td>
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<td>17 patients with treatment-resistant MD received psychological support (without psychotherapy) and a single ayahuasca dose (0.8 mg/mL DMT)</td>
<td>Ayahuasca was well tolerated</td>
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<td>Palhano-Fontes et al., 2019</td>
<td>Brazil, randomized, double-blind, placebo-controlled, parallel-group</td>
<td>Significant reductions in depression (HAMD, MADRS, BPRS) at 40 to 180 minutes and at the 1-day and 1-, 2-, and 3-week follow-ups ($P &lt; .05$)</td>
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<td>29 patients with treatment-resistant MD received psychological support (without psychotherapy) and a single ayahuasca dose (0.36 mg/mL DMT)</td>
<td>Ayahuasca was well tolerated</td>
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<td>Davis et al., 2020</td>
<td>United States, open-label (waiting list-controlled)</td>
<td>Significant reductions in depression (GRID, BDI, PHQ) at 1-day to 4-week follow-ups (full sample compared to baseline and between-group differences) ($P &lt; .05$)</td>
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<td>24 patients with MD received psychological support/psychotherapy and two psilocybin doses (20 and then 30 mg/70 kg, mean of 1.6 weeks apart) (the waiting list groups received psilocybin treatment 8 weeks after the immediate treatment group)</td>
<td>Significant reductions in anxiety (STAI, HAM-A) at the 4-week follow-up (full sample compared to baseline) ($P &lt; .05$)</td>
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<td>Psilocybin was well tolerated</td>
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</tbody>
</table>

BDI: Beck Depression Inventory; BPRS: Brief Psychiatric Rating Scale; BSI: Brief Symptom Inventory; DMT: dimethyltryptamine; GRID: GRID-Hamilton Depression Rating Scale; HADS: Hospital Anxiety and Depression Scale; HAM-A: Hamilton Anxiety Rating Scale; HAM-D: Hamilton Depression Rating Scale; LSD: lysergic acid diethylamide; MADRS: Montgomery–Asberg Depression Rating Scale; MD: major depression; PHQ: Patient Health Questionnaire; POMS: Profile of Mood States; QIDS: Quick Inventory of Depressive Symptoms; STAI: State-Trait Anxiety Inventory.
Possible mechanisms

Preclinical studies

Preclinical studies consistently suggest that the main mechanism of action of psychedelics is agonism at cortical layer V pyramidal 5-HT$_{2A}$ receptors (López-Giménez and González-Maeso, 2018; Nichols, 2004, 2016). For instance, studies in animals show that administration of 5-HT$_{2A}$ receptor antagonists block most of the behavioral effects of these drugs (Halberstadt, 2015; López-Giménez and González-Maeso, 2018; Marek, 2018; Nichols, 2004, 2016). At the molecular level, activation of the 5-HT$_{2A}$ receptor increases glutamatergic tone and activation of the alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic (AMPA) glutamate receptors, BDNF’s high-affinity receptor (tyrosine kinase B receptor, TrkB), and the mammalian target of rapamycin (mTOR). These effects converge into increases in BDNF expression, neuritogenesis, spinogenesis, and synaptogenesis in the PFC (dos Santos et al., 2016; Ly et al., 2018; Marek, 2018; Nichols, 2004, 2016; Nutt et al., 2020; Olson, 2018). Such enhanced neuroplasticity is also produced by ketamine and is currently thought to be one of the main mechanisms involved in its antidepressant effects (Ly et al., 2018; Olson, 2018). Compounds like ketamine and serotoninergic psychedelics that produce such effects on neural plasticity have been labeled ‘psychoplastogens’ (Olson, 2018).

Other mechanisms of psychedelics could be related to the role of 5-TH$_{2A}$ cortical receptors in improving memory and learning (thus cognitive flexibility) in depression (Harvey, 2003; Morales-Garcia et al., 2020; Zhang and Stackman, 2015). For instance, a core depressive symptom is rumination, or a rigid pattern of negative thinking about oneself and the world. Rumination is associated with increased default mode network (DMN) activation, and acute administration of psychedelics deactivates the DMN (Carhart-Harris et al., 2012; Palhano-Fontes et al., 2015; Pasquini et al., 2020; Smigielski et al., 2019; see for review dos Santos et al., 2016). This could create an opportunity to re-learn new patterns of thought and thus increase cognitive flexibility. This relates well to the effects of these compounds on neuroplasticity. On the molecular level, these re-learning effects could be related to a decrease in 5-HT$_{2A}$ receptor signaling (Harvey, 2003; Zhang and Stackman, 2015), a pathway shared by several antidepressants. Repeated administration of psychedelics induces 5-HT$_{2A}$ receptor desensitization (Romano et al., 2010; Roth et al., 1995), decreased signaling (Greshc et al., 2005), and downregulation (Aloyo et al., 2001; Smith et al., 1999). Desensitization of hippocampal 5-HT$_{2A}$ receptors produced by repeated LSD administration was reported to be associated with enhanced learning (Romano et al., 2010; see for review Harvey, 2003; Zhang and Stackman, 2015) and with reduced hippocampal 5-HT$_{2A}$ receptor signaling and normalization of learning in an animal model of depression (Buchhorn et al., 2014). In line with and even more relevant to the human model of single/few doses of these drugs required in clinical trials, a cell-line study showed that desensitization can occur rapidly (24 h) and without downregulation (Roth et al., 1995). Related to 5-HT$_{2A}$ receptor decreased signaling is the fact that the psychedelics act as partial agonists and thus can also behave as functional (not full) antagonists at the receptor level. Moreover, different effects downstream of receptor activation (such as gene expression) compared with non-hallucinogenic 5-HT$_{2A}$ receptor agonists could also explain part of the beneficial effects of these compounds (González-Maeso and Sealfon, 2009; López-Giménez and González-Maeso, 2018).

Human studies

Human studies show that administration of 5-HT$_{2A}$ receptor antagonists blocks most of the subjective effects of psychedelics (see for review dos Santos and Hallak, 2020; dos Santos et al., 2016; Marek, 2018). 5-HT$_{2A}$ receptors are expressed in brain regions involved in perception, emotion processing, memory, and self-awareness, including the PFC, ACC, and the amygdala (dos Santos and Hallak, 2020; dos Santos et al., 2016; Nichols, 2004, 2016; Nutt et al., 2020). Neuroimaging studies with healthy volunteers using radiotracers show that these psychedelics increase excitatory tone in the frontotemporal/fronomedial cortex, medial temporal lobe, and occipital cortex, while functional studies show that they decrease functional connectivity (FC) in key hubs of the DMN and also reduce amygdala reactivity to threat (dos Santos and Hallak, 2020; dos Santos et al., 2016; Nutt et al., 2020). Such effects are accompanied by disruptions of neural hierarchies and enhanced brain entropy (dos Santos et al., 2016; Nutt et al., 2020). In an open-label trial of psilocybin in TRD, psilocybin reduced the reaction time to face recognition and increased amygdala activation to these faces, effects which were predictive of antidepressant effects (Roseman et al., 2018; Stroud et al., 2018). Moreover, decreased PFC-amygdala FC during face processing was associated with rumination levels 1 week after psilocybin intake (Mertens et al., 2020). These results suggest that the antidepressant effects of psilocybin are related to increases in emotional responsiveness. However, due to the open-label design of the trial, controlled trials are needed to corroborate these findings.

In the case of ayahuasca, while DMT increases neuritogenesis, spinogenesis, and synaptogenesis (Ly et al., 2018), the β-carboline harmine increases hippocampal BDNF levels and stimulates neurogenesis, suggesting a possible synergistic effect of these ayahuasca alkaloids (dos Santos and Hallak, 2020). In the controlled trial of ayahuasca and TRD, compared to placebo ayahuasca intake increased BDNF levels 48h later, and a negative correlation between serum BDNF levels and depressive symptoms was observed (de Almeida et al., 2019). Ayahuasca’s effects on BDNF levels were modulated by acute increases in cortisol levels (Galvão et al., 2018), and ayahuasca also reduced inflammatory C-reactive protein, which was correlated to its antidepressant effects (Galvão-Coelho et al., 2020). These results suggest a cross-talk between BDNF, cortisol, and inflammatory markers in the antidepressant effects of ayahuasca. Recent studies with healthy volunteers showed that LSD doses of 5 and 20 µg (Hutten et al., 2020) and 200 µg (Holze et al., 2020) acutely increased BDNF plasma levels. Interestingly, LSD doses of 10 µg (Hutten et al., 2020) and 25, 50, and 100 µg (Holze et al., 2020) did not alter BDNF levels. The effects of psychedelics on BDNF levels should be further explored in both healthy volunteers and patients with psychiatric disorders to better understand the dose-effects of these drugs on variation of BDNF levels and the link between BDNF and antidepressant response.

Psychotherapeutic techniques could also enhance the antidepressant and anxiolytic effects of psychedelics. Indeed, in the 1950s to 1970s the therapeutic effects of these compounds were explained/understood more in psychological terms, and most
studies were performed in a psychotherapeutic context. However, accumulating evidence from recent molecular, behavioral, and neuroimaging studies suggest that these effects also have a biological basis. Indeed, in the open-label (Sanches et al., 2016) and controlled (Palhano-Fontes et al., 2019) trials with ayahuasca and TRD no psychotherapy was used, and the open-label trial with psilocybin and TRD (Carhart-Harris et al., 2016) only used ‘psychological support’. The controlled trials of psilocybin (Griffiths et al., 2016; Grob et al., 2011; Ross et al., 2016) and LSD (Gasser et al., 2014) for depression and anxiety in life-threatening diseases/cancer and the wait list-controlled trial of psilocybin for MDD (Davis et al., 2020) used elaborate psychotherapeutic techniques. Therefore, the role of psychotherapy in psychedelic research is still unknown, and future studies should compare the effects of these drugs with and without such interventions.

Conclusions
Depression is a major cause of suffering worldwide, and current treatments are not effective for a significant proportion of patients. Together with reports of the fast-acting and enduring antidepressant effects of ketamine, the observation of such effects produced by psychedelics are among the most recent exciting discoveries in modern psychiatry. It is important that the scientific community optimistically reopen the doors to the possible clinical use of these compounds, keeping in mind that such investigations must be done by recognized, credible researchers and that detailed records must be kept of side effects as well as beneficial effects.

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