Rapid antidepressant effects of the psychedelic ayahuasca in treatment-resistant depression: a randomised placebo-controlled trial

Fernanda Palhano-Fontes[1,2], Dayanna Barreto[2,3], Heloisa Onias[1,2], Katia C Andrade[1,2], Morgana Novaes[1,2], Jessica A Pessoa[1,2], Sergio A Mota-Rolim[1,2], Flavia Osório[4,5], Rafael Sanches[4,5], Rafael G dos Santos[4,5], Luís F Tófoli[6], Gabriela de Oliveira Silveira[7], Mauricio Yonamine[7], Jordi Riba[8], Francisco RR Santos[9], Antonio A Silva-Junior[9], João Alchieri[10], Nicole L Galvão-Coelho[5,11], Bruno Lobão-Soares[5,12], Jaime Hallak[4,5], Emerson Arcoverde[2,3,5], João P Maia-de-Oliveira[2,3,5], Dráulio B Araújo[1,21].

[1]Brain Institute, Federal University of Rio Grande do Norte (UFRN), Natal, Brazil, [2]Onofre Lopes University Hospital, Federal University of Rio Grande do Norte (UFRN), Natal, Brazil; [3]Dept. of Clinical Medicine, Federal University of Rio Grande do Norte (UFRN), Natal, Brazil; [4]Dept. of Neurosciences and Behaviour, University of Sao Paulo (USP), Ribeirão Preto, Brazil; [5]National Institute of Science and Technology in Translational Medicine (INCT-TM), Brazil; [6]Dept. of Psychiatry, University of Campinas (UNICAMP), Campinas, Brazil; [7]Dept. of Clinical Analysis and Toxicology, University of Sao Paulo (USP), São Paulo, Brazil; [8]Sant Pau Institute of Biomedical Research, Barcelona, Spain; [9]Dept. of Pharmacy, Federal University of Rio Grande do Norte (UFRN), Natal, Brazil; [10]Dept. of Psychology, Federal University of Rio Grande do Norte (UFRN), Natal, Brazil; [11]Dept. of Physiology, Federal University of Rio Grande do Norte (UFRN), Natal, Brazil; [12]Dept. of Biophysics and Pharmacology, Federal University of Rio Grande do Norte (UFRN), Natal, Brazil.

Abstract

Major Depressive Disorder affects about 350 million people worldwide, and about one-third of the patients are considered treatment-resistant. Furthermore, available antidepressants take usually two weeks for the onset of their antidepressant effect. Recent open label trials show that psychedelics, such as ayahuasca and psilocybin, hold promise as fast-onset antidepressants. Although promising, these studies were not controlled for the placebo effect. To address this issue, and to further test the antidepressant effects of ayahuasca, we conducted a parallel arm, double-blind randomised placebo-controlled trial, in patients with treatment-resistant major depression. Thirty-five patients with treatment-resistant major depression received a single dose of ayahuasca or placebo. We measured as primary outcome the change in the Hamilton Depression Rating scale (HAM-D) seven days after the dosing session, and as secondary outcomes the changes in Montgomery–Åsberg Depression Rating Scale (MADRS), and response rates at one day (D1), two days (D2) and seven days (D7) after dosing, and remission rates at D7. This study is registered with http://clinicaltrials.gov (NCT02914769). We observed robust evidence of rapid antidepressant effects of a single dosing session with ayahuasca when compared to placebo. HAM-D scores at D7 were significantly lower in patients treated with ayahuasca than in those treated with placebo ($p=0{\cdot}019$; Cohen's $d=0{\cdot}98$). MADRS scores were significantly reduced in the ayahuasca group compared to the placebo group at all endpoints (at D1 and D2, $p=0{\cdot}04$; at D7, $p<0{\cdot}0001$). Between-group effect sizes increased from D1 to D7 (D1: Cohen's $d=0{\cdot}84$; D2: Cohen's $d=0{\cdot}84$; D7: Cohen's $d=1{\cdot}49$). Response rates were high for both groups at D1 and D2, and were significantly higher in the ayahuasca group only at D7 (64% vs. 27%; OR = 4·95; p = 0·04; NNT = 2·66). Remission rate was not significantly different between groups. Our study provides new evidence of rapid antidepressant effects of ayahuasca for treatment-resistant major depression.

[1]Corresponding author: prof. Dráulio B. de Araújo.
Brain Institute (UFRN). Av. Nascimento Castro, 2155 59.056-560 – Natal, RN – Brazil. Email: draulio@neuro.ufrn.br

Introduction

The World Health Organization estimates that about 350 million people suffer from depression, and about one-third do not respond to appropriate courses of at least three antidepressants.[1-3] On the other hand, most antidepressants are based on discoveries made in the 1950s (of monoamine oxidase inhibitors and tricyclic antidepressants), or in the 1980s (of selective serotonin reuptake inhibitors). They all share a similar efficacy profile, common mechanisms of action based on the modulation of brain monoamines, and it often takes about two weeks for the onset of their antidepressant effect.[1,3]

Recent evidence, however, show a rapid and significant antidepressant effect of the dissociative substance ketamine, a N-methyl-D-aspartate (NMDA) antagonist frequently used in anaesthesia[4]. Randomised placebo-controlled trials in treatment-resistant depression show a peak of antidepressant effects of ketamine one day after dosing, which remain significant for about seven days.[4]

On the other hand, research with serotonergic psychedelic substances has gained momentum.[5] A few centres around the world are currently exploring how these substances interact with the brain, and probing their potential use in treating different psychiatric conditions, including mood disorders.[6-11] Recent open label trials show that psychedelics, such as ayahuasca and psilocybin, hold promise as fast-onset antidepressants in treatment-resistant patients.[7-9]

Ayahuasca is a brew traditionally used by indigenous populations of the Amazon Basin for healing and spiritual purposes. In the 1930s it began to be used in religious settings of Brazilian small urban centres, reaching large cities in the 1980s and expanding since then to several other parts of the world.[12] In Brazil, ayahuasca has a legal status for ritual use since 1987. Ayahuasca is a decoction of two plants: *Psychotria viridis* that contains the psychedelic N,N-dimethyltryptamine (DMT), a serotonin and sigma-1 receptors agonist,[13] and *Banisteriopsis caapi*, rich in the reversible monoamine oxidase A inhibitors: harmine, harmaline, and tetrahydroharmine.[14,15]

The acute psychological effects of ayahuasca last ~4h, and are related to intense perceptual, cognitive and affective changes.[14-16] Although nausea, vomiting and diarrhoea are frequently reported, mounting evidence points to a positive safety profile of ayahuasca. It is not addictive, and it has not been associated with psychopathological, personality or cognitive deterioration, promoting only moderate sympathomimetic effects.[15-19] The main concern related to this class of substances refers to rare instances of prolonged increases in psychotomimetic symptoms, especially in individuals prone to psychosis.[20]

In a recent open label trial, 17 patients with major depressive disorder attended a single dosing session with ayahuasca. Depression severity was assessed before, during and after dosing by the Hamilton Depression Rating Scale (HAM-D) and the Montgomery–Åsberg Depression Rating Scale (MADRS). We found a significant reduction in depression severity already at the first hours after dosing, an effect that remained significant for 21 days.[7,8]

Although promising, these studies have not controlled for the placebo effect, which can be remarkably high. In clinical trials for depression the placebo effect can reach 35-40%.[21] To address this issue, and to further test the antidepressant effects of ayahuasca, we conducted a parallel arm, double-blind randomised placebo-controlled trial, in patients with treatment-resistant major depression.

Methods

This study was a double-blind randomised placebo-controlled trial using a parallel arm design. Patients were recruited from psychiatrist referrals from local outpatient psychiatric units or through media and Internet advertisements. All procedures took place at the Onofre Lopes University Hospital (HUOL), Natal-RN, Brazil. The study was approved by the University Hospital Research Ethics Committee (# 579.479). All subjects provided written informed consent before participation. This study is registered with http://clinicaltrials.gov (NCT02914769).

We recruited adults aged 18-60 years who met criteria for unipolar major depressive disorder as diagnosed by the Structured Clinical Interview for Axis I (DSM-IV). Only treatment-resistant patients were selected, defined herein as those with inadequate responses to at least two antidepressant medications from different classes.[2] Selected patients were in a current depressive episode of moderate-to-severe at screening (HAM-D≥17). We adopted the following exclusion criteria: previous experience with ayahuasca; current medical disease based on history, physical examination and routine hematologic and

biochemical tests; pregnancy; current or previous history of neurological disorders, psychosis, schizophrenia or bipolar affective disorder; history of mania or hypomania; use of substances of abuse; and suicidal risk.

Patients were randomly assigned (1:1) to receive ayahuasca or placebo, using permuted blocks of size 10. All investigators and patients were blind to intervention assignment, which was kept only in the database and with the pharmacy administrators. Masking was further achieved by ensuring that all patients were naïve to ayahuasca, and by randomly assigning a different psychiatrist for patient follow-up assessments. Both ayahuasca and placebo were kept in identical amber glass bottles.

The substance used as placebo was an inert liquid produced by the Department of Pharmacy (UFRN), and designed to simulate the organoleptic properties of ayahuasca, such as a bitter and sour taste, and a brownish colour. It contained water, yeast, citric acid, zinc sulphate and a caramel colorant. A single ayahuasca batch was used throughout the study. The batch was prepared and provided free of charge by a branch of the Barquinha church based in the city of Ji-Paraná, Brazil.

To assess alkaloids concentrations and stability of the batch, samples of ayahuasca at two different moments, one in each year of data acquisition, were sent to the Department of Clinical Analysis and Toxicology (USP) for mass spectroscopy analysis. On average, the ayahuasca used contains (mean ± SD): 0·36±0·01 mg/mL of DMT, 1·86±0·11 mg/mL of harmine, 0·24±0·03 mg/mL of harmaline, and 1·20±0·05 mg/mL of tetrahydroharmine.

After screening, recruited patients underwent a washout period adjusted to the half-life time of their current antidepressant medication. It lasted from one to four weeks, but typically lasted two weeks.

All patients were enrolled in a series of tests and assessments, conducted in the course of a four-day experimental session, to assess changes in different markers of depression. One day before and one day after dosing patients were submitted to psychiatric evaluation, structural and functional magnetic resonance imaging (MRI), neuropsychological tests, biochemical tests, sleep electroencephalography (EEG) and questionnaires (these data will be reported elsewhere).

During the experimental session, patients were not under any antidepressant medication. If needed, benzodiazepines were allowed as a supporting hypnotic and/or anxiolytic agents. A new treatment scheme was proposed 7 days (D7) after dosing.

Baseline assessments occurred one day before dosing, and included psychiatric, MRI, neuropsychological and sleep EEG evaluations. Next day, early morning, we collected baseline fasting blood and saliva samples. After a light breakfast, patients were prepared for the dosing session, with baseline psychiatric evaluation and EEG verification.

Dosing sessions lasted approximately 8 hours, and most often occurred between 8:00 and 16:00. They took place in a quiet and comfortable living room-like environment, with a bed, a recliner, with controlled temperature, natural and dimmed light. Immediately before dosing, patients were prepared with instructions and orientations about the effects they could experience, and strategies to help alleviating eventual difficulties. Intake occurred around 10:00.

Patients received a single dose of ayahuasca containing 0·36 mg/kg of DMT, or 1 ml/kg of placebo. They were asked to remain quiet, with their eyes closed, while focusing on their body, thoughts and emotions. They were also allowed to listen to a predefined music playlist. Patients received support throughout the session from at least two investigators who stayed in a room next door, offering assistance when needed.

Electrophysiological data were continuously recorded during the dosing session with a 32-channel system (Brain Products, EasyCap, Herrsching-Breitbrunn, Germany), and included electroencephalography (EEG), electrooculography (EOG), electrocardiography (ECG), and electromyography (EMG) measurements (these data will be reported elsewhere).

The Clinician-Administered Dissociative States Scale (CADSS) and the Brief Psychiatric Rating Scale (BPRS) were applied at baseline, 1:40h, 2:40h and 4:00h after intake. We also collected saliva samples at these time points.

When the acute psychedelic effects had ceased, patients were debriefed on their experience, and had a final psychiatric evaluation. Around 16:00 they could go home accompanied by a relative or friend. Patients with severe depression at baseline remained as inpatients at the hospital ward for the entire week.

One day after dosing (D1), patients returned to the

hospital for post-dosing assessments (psychiatric, MRI, neuropsychology, questionnaires), and the second sleep-EEG evaluation. Next day morning, new blood and saliva samples were collected, and participants were encouraged to describe their experience once more. Around 09:00, after psychiatric evaluation, they were discharged.

After the experimental session, patients were asked to return for eight follow-up assessments: seven days (D7), when a new commercially available antidepressant medication was prescribed, 14 days and monthly until six months (M6) after dosing (these data will be reported elsewhere).

The primary outcome measure was the change in depression severity assessed by the HAM-D scale, comparing baseline (one day before) with seven days (D7) after dosing. Secondary outcome was the change in MADRS scores from baseline to one day (D1), two days (D2) and seven days after dosing (D7). In order to assess efficacy, we examined the proportion of patients meeting response criteria at D1, D2 and D7, defined as a reduction of 50% or more in baseline scores. Remission rates, defined as HAM-D≤7 and MADRS≤10, were also examined at D7. These endpoints were chosen to allow comparison with previous studies of ketamine for treatment-resistant major depression,[4] and to avoid interaction with the new antidepressant medication prescribed. Safety and tolerability were also assessed and included dissociative and psychotomimetic evaluation using CADSS and BPRS–Positive Subscale (BPRS+) during the dosing session.

Analyses adhered to a modified intent-to-treat principle, including all patients who complete dosing and D7 assessments. An estimated sample size of 42 patients is needed to provide 80% power to detect a 5-point HAM-D difference (standardized effect size=0·9) for differences of ayahuasca and placebo between baseline and D7 with two-sided 5% significance. Changes in HAM-D scores were examined by analysis of covariance (ANCOVA): scores at D7 were used as the dependent variables, ayahuasca or placebo as independent variables, and the baseline scores as covariate. Due to missing values (4 points), changes in MADRS scores were inspected with a fixed-effects linear mixed model including D1, D2 and D7 scores as dependent variables and the baseline scores as covariate. A Toeplitz covariance structure was the best fit to the data according to Akaike's information criterion. Missing data were estimated using restricted maximum likelihood estimation. Main effects and treatment vs. time interaction were evaluated. Post-hoc t-tests were performed for between-groups comparisons at all endpoints, and Sidak's test was used to control for multiple comparisons. Significance was evaluated at $p < 0{\cdot}05$, two-tailed. Cohen's d effect sizes were obtained for two different comparisons. For between-group, they were calculated using the estimated means of each group at each endpoint. For within-group comparisons, effects sizes of each treatment were calculated separately, using the differences between an endpoint and baseline values. Evaluation of efficacy was based on the proportion between responders/non-responders and remitters/non-remitters in each group, using Fisher's exact test. Odds ratio (OR) and number needed to treat (NNT) were also calculated. Data from patients who reduced their HAM-D or MADRS scores by 50% or more between washout onset and baseline assessment, or were in remission in the day of dosing were not considered for statistical analysis. We used IBM SPSS Statistic 20 and Prism 7 to run the analyses.

Results

Figure 1 shows the trial profile. From January 2014 to June 2016, we assessed 218 patients for eligibility, and 35 met criteria for the trial. Six were not included in the analysis: five no longer met criteria for depression in the day of dosing, and one dropped out before dosing. Data from 29 patients were included in the analysis: 14 in the ayahuasca group and 15 in the placebo group.

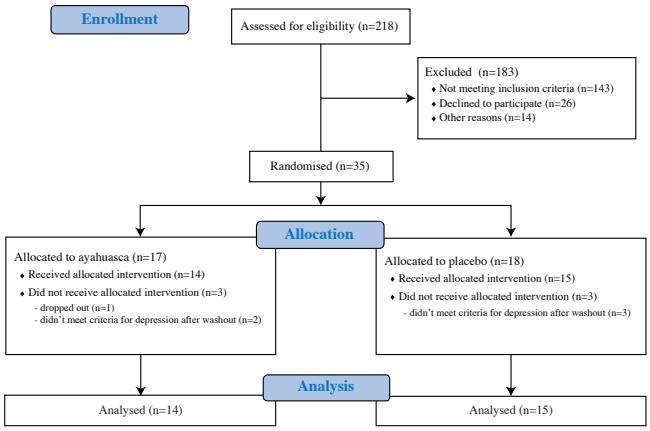

Figure 1. Trial profile.

On average, patients met criteria for moderate-to-severe depression (mean±SD): HAM-D = 21·83 ± 5·35; MADRS = 33·03 ± 6·49. They had been experiencing depressive symptoms for 11·03 ± 9·70 years, and had tried 3·86 ± 1·66 different previous unsuccessful antidepressant medications. Two patients had previous history of electroconvulsive therapy (ECT). Most patients (76%) had a comorbid personality disorder, and 31% had comorbid anxiety disorder. All patients were under regular use of benzodiazepines.

All patients were Brazilian, mostly female (72%) adults (42·03 ± 11·66 yo), from low socioeconomic status backgrounds: low educated (<8 years of formal education) and living on low household incomes (<2 minimum wages). No significant differences were found between groups in socio-demographic characteristics.

Figure 2 shows changes in HAM-D scores from baseline to seven days after dosing (D7). ANCOVA analysis shows a significant difference between groups at D7 (F_1=6·31; p=0·019) with patients treated with ayahuasca presenting less severity when compared to patients treated with placebo. Between-group effect size is large at D7 (Cohen's d=0·98; CI 95%:0·21 to 1·75).

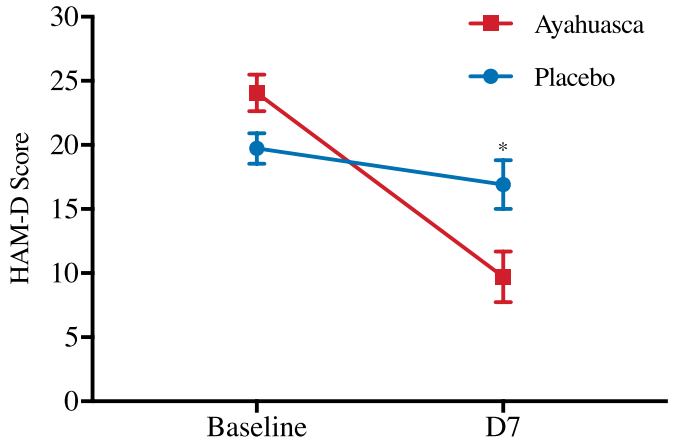

Figure 2. HAM-D scores at baseline and seven days (D7) after dosing. Estimated means are expressed as mean ± SEM. ANCOVA analysis shows a significant difference between ayahuasca (red squares) and placebo (blue circles) at D7 (p=0·019). Effect size (Cohen's d) for this difference is 0·98 (CI 95%:0·21 to 1·75). Asterisk indicates significance level between-group (*p<0·05). HAM-D scores: mild depression (8–16), moderate (17–23), severe (≥24).

The response rate is significantly different at D7, with 57% of responders in the ayahuasca group against 20% in the placebo group (OR=5·33 [95% CI: 1·11 to 22·58]; p=0·04; NNT=2·69). Remission was not significantly different between groups: 43% in ayahuasca vs. 13% in placebo (OR=4·87 [95% CI: 0·77 to 26·73]; p=0·07; NNT=3·39).

Figure 3 shows MADRS scores estimated means as a function of time. The linear mixed model indicates a significant effect for time ($F_{2,34\cdot4}$=3·96; p=0·028), treatment ($F_{1,27\cdot7}$=10·52; p=0·003) and no treatment vs. time interaction ($F_{2,34\cdot4}$=1·77; p=0·185) (Fig. 3). Post-hoc analysis shows a significant difference between groups at all endpoints: at D1 ($F_{1,49\cdot7}$=4·58; p=0·04), D2 ($F_{1,50\cdot3}$ = 4·67; p=0·04) and D7 ($F_{1,47}$=14·81; p<0·0001). Effect size between groups is large at D1 (Cohen's d=0·84; CI 95%: 0·05 to 1·62) and D2 (Cohen's d=0·84; CI 95%: 0·05 to 1·63) and largest at D7 (Cohen's d=1·49; CI 95%: 0·67 to 2·32).

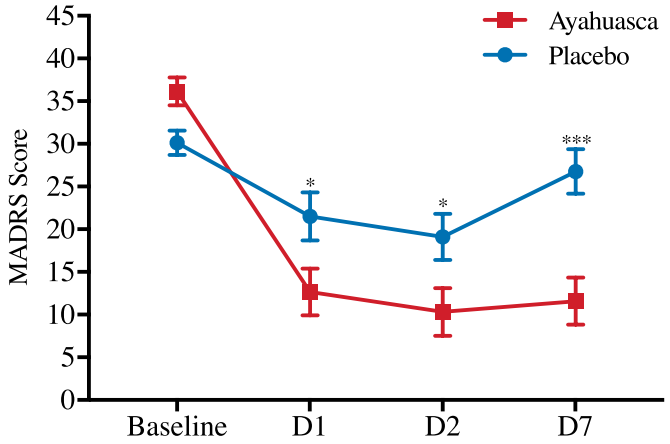

Figure 3. Average MADRS scores as a function of time. Baseline means (± SEM) and estimated marginal means (± SEM) for all endpoints for the ayahuasca (red squares) and placebo groups (blue circles). Between groups comparisons show significant differences at D1 (p=0·04), D2 (p=0·04) and D7 (p<0·0001). Between groups effect sizes are: D1 (Cohen's d=0·84), D2 (Cohen's d=0·84) and D7 (Cohen's d=1·49). Asterisks indicate significance level of between-groups (*p<0·05; ***p<0·0001). MADRS scores: mild depression (11–19), moderate (20–34), severe (≥34).

Figure 4 shows the response rate as a function of time. At D1, response rates were high for both groups: 50% in the ayahuasca group, and 46% in the placebo group (OR=1·17 [95% CI: 0·26 to 5·48]; p=0·87;

NNT=26). At D2 we found response rates of 77% for ayahuasca and 64% for placebo (OR=1·85 [95% CI: 0·29 to 8·40]; p=0·43; NNT=7·91). A significantly different response rate was only observed at D7, with 64% of responders in the ayahuasca group, against 27% in the placebo group (OR=4·95 [95% CI: 1·11 to 21·02]; p=0·04; NNT=2·66). Remission rate was not significantly different between groups: 36% in the ayahuasca group, against 8% in the placebo group (OR=6·11 [95% CI: 0·81 to 77·48]; p=0·09; NNT=3·65).

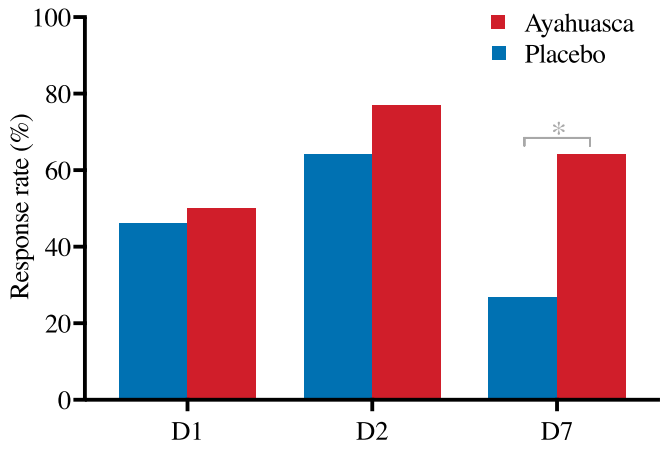

Figure 4. Response rate as a function of time. At **D1-** ayahuasca (50%), placebo (46%); **D2-** ayahuasca (77%), placebo (64%); **D7-** ayahuasca (64%), placebo (27%). Treatment responses were different only at D7 (OR=4·95 [95% CI: 1·11 to 21·02]; p=0·04; NNT=2·66).

The most frequently observed adverse effects included nausea (71%), vomiting (57%), transient anxiety (50%), transient headache (42%), and restlessness (50%). Patients presented transient dissociative and psychotomimetic symptoms as measured by CADSS and BPRS+ scales, showing increased scores (not significant) 1h40 after ayahuasca intake: 34·8% (BPRS+) and 21·6% (CADSS).

Discussion

We found robust evidence of rapid antidepressant effects after a single dosing session with ayahuasca, when compared to placebo. Depression severity changed significantly but differently for the ayahuasca and placebo groups. At all endpoints, improvements observed in the ayahuasca group were significantly higher than those of the placebo group, with increasing between-group effect sizes between D1 and D7. Response rates were high for both groups at D1 and D2, and were significantly higher in the ayahuasca group only at D7.

The within-group effect size found for ayahuasca at D7 (Cohen's d=2·22) is compatible with our earlier open label study with seventeen patients (Cohen's d: D7=1·83).[8] However, it is smaller than an equivalent measure recently found in an open label trial for depression with psilocybin (Hedges' g=3·1).[9]

Although both ketamine and ayahuasca are associated with rapid antidepressant effects, their response time-courses and mechanisms of action seem to be different. Nevertheless, it is noteworthy that analogous to ketamine, serotonergic psychedelics have recently been shown to modulate glutamatergic neurotransmission.[22] Pooled analysis from four studies with ketamine for treatment-resistant unipolar depression reveals the largest between-group effect size at D1 (Cohen's d=0.89), reducing towards D7 (Cohen's d=0.41).[4] In contrast, the effect sizes observed for ayahuasca were smallest at D1 (Cohen's d=0·84), and largest at D7 (Cohen's d=1·49). These differences are also reflected in the response rate. At D1, the response rate to ketamine lies between 37-70%,[4] whereas 50% of the patients responded to ayahuasca. At D7, the ketamine response rate lies between 7-35%,[4] in comparison to 64% for ayahuasca.

The placebo effect was high in our study, and higher than most studies with ketamine.[4] While in our study the response rate to placebo is 46% at D1, and 26% at D7, ketamine trials have found a placebo effect on the order of 0-6% at D1, and 0-11% at D7.[4] The high placebo effect observed here may be related to the low socioeconomic status of most of our patients, who were living under significant psychosocial stressors.[23] Our trial involved a four-day stay at a very comfortable and supportive environment, configuring a particularly pleasant place for our patients, which might have an impact on the observed placebo response. Besides, comorbid personality disorders were found in 76% of our patients, most of them (90%) in cluster B (DSM IV), which have been associated to higher placebo responses, worse prognosis and poorer treatment response.[3,24]

A growing body of evidence gives support to the observed rapid antidepressant effects of ayahuasca. The sigma-1 receptor (σ1R) is activated by DMT, and it has been implicated in depression.[1,13] For instance, it has been

shown that the administration of σ1R agonists results in antidepressant-like effects which are blocked by σ1R antagonism.[1,3] Furthermore, σ1R upregulates neurotrophic factors such as brain derived neurotrophic factor (BDNF) and nerve growth factor (NGF), proteins whose regulation and expression seem to be involved in the pathophysiology and treatment of depression.[1,3]

Moreover, several studies in animal models observed that chronic administration of harmine reduces immobility time, increases climbing and swimming time, reverses anhedonia, increases adrenal gland weight, and increases BDNF levels in the hippocampus.[25] All of these are compatible with antidepressant effects. A recent study in rodents found that a single ayahuasca dose increased swimming time in a forced-swim test, which is considered an antidepressant-like behavioural effect.[26] Likewise, harmine seems to stimulate neurogenesis of human neural progenitor cells, derived from pluripotent stem cells, a mechanism also observed in rodents following antidepressant treatment.[27]

Over the last two decades, mental health evaluations of regular ayahuasca consumers have shown preserved cognitive function, increased well-being, reduction of anxiety, and depressive symptoms when compared to non-ayahuasca consumers.[17,18] Moreover, a recent study showed that a single dose of ayahuasca enhanced mindfulness-related capacities,[28] which could help to understand the antidepressant effects of ayahuasca since meditation practices have also been related to antidepressant effects.[29]

Brain circuits modulated by psychedelics show great overlap with those involved in mood disorders.[5] We recently found that a single ayahuasca session in patients with depression increased blood flow in brain regions consistently implicated in the regulation of mood and emotions,[3] such as the left nucleus accumbens, right insula and left subgenual area.[8] Furthermore, we have recently found that ayahuasca reduces the activity of the Default Mode Network (DMN),[30] a brain network consistently found to be hyperactive in depression, presumably due to rumination often observed in these patients.[3]

No serious adverse effects were observed during or after the dosing session. Although 100% of the patients reported feeling safe during the ayahuasca session, it was not necessarily a pleasant experience. In fact, some patients reported the opposite, as the experience was accompanied by psychological distress. Most patients reported nausea, and about 57% have vomited, although vomiting is traditionally not considered a side effect of ayahuasca, but rather part of a purging process.[16]

This study has some limitations. The number of participants is modest, and therefore randomised trials in larger populations are necessary. Moreover, this study was limited to patients with treatment-resistant depression, with long course of illness, and high comorbid personality disorder, which precludes a simple extension of these results to other classes of depression.

Since the prohibition of psychedelics in the late 1960s, research with these substances has almost come to a halt. Before research restrictions, psychedelics were at early stage testing for many psychiatric conditions, including obsessive-compulsive disorder and alcohol dependence. By mid 1960s, over 40.000 subjects had participated in clinical research with psychedelics, most of them in uncontrolled settings.[5] To our knowledge this is the first randomised placebo-controlled trial to investigate the antidepressant potential of a psychedelic in a population of patients with treatment-resistant depression. Overall, this study brings important new evidence supporting the safety and therapeutic value of psychedelics, dosed within an appropriate setting, to be used as a tool to help treating different human mental conditions.

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